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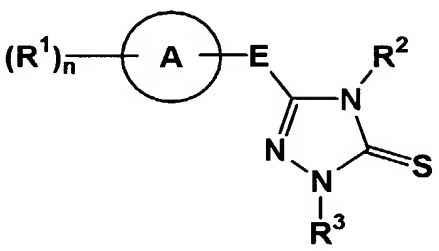
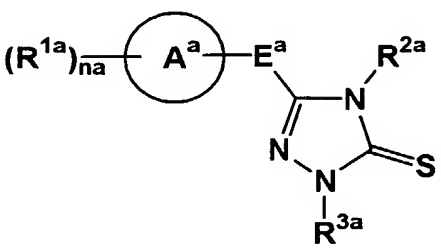
(54) Title: 4H-1,2,4-TRIAZOLE-3(2H)-THIONE DERATIVES AS SPHINGOMYELINASE INHIBITORS



(I)



(Ia)

(57) Abstract: A neutral sphingomyelinase inhibitor of formula (I) and a novel compound of formula (Ia). Wherein all groups have the same meaning as defined in the claim.A compound of formula (I) is applicable for medicaments for the treatement and/or prevention of the diseases associated with disorders of neutral sphingomyelinase.

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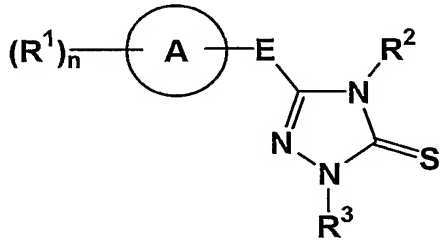
DESCRIPTION

4H-1,2,4-TRIAZOLE-3(2H)-THIONE DERATIVES AS SPHINGOMYELINASE INHIBITORS

TECHNICAL FIELD

This invention relates to 4H-1,2,4-triazole-3(2H)-thione derivatives and neutral sphingomyelinase inhibitors containing 4H-1,2,4-triazole-3(2H)-thione derivatives as active ingredient. More particularly, this invention relates to;

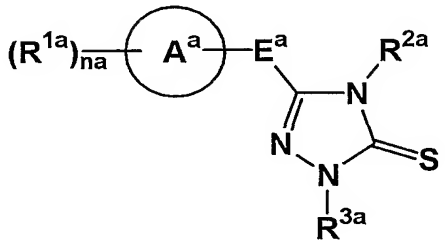
1) neutral sphingomyelinase inhibitors comprising 4H-1,2,4-triazole-3(2H)-thione derivatives of formula (I)



(I)

wherein all symbols have the same meaning as hereinafter described,

2) novel 4H-1,2,4-triazole-3(2H)-thione derivatives of formula (Ia)



(Ia)

wherein all symbols have the same meaning as hereinafter described, and

3) processes for the preparation of the compounds of formula (Ia).

BACKGROUND ART

Sphingomyelin and its metabolic products are known to play a role as second messengers in a variety of cellular signaling pathways. Sphingomyelinases (SMase) cleave sphingomyelin to produce ceramide and phosphocholine. Ceramide serves as a

second messenger that induces a variety of cell regulatory phenomena such as apoptosis, cell differentiation, cell proliferation, and sterol homeostasis. Neutral SMase (N-SMase) is a Mg^{2+} sensitive enzyme that can be activated by a host of physiologically relevant and structurally diverse molecules like tumor necrosis factor-alpha (TNF-alpha), oxidized low density lipoproteins (Ox-LDL), and several growth factors. Programmed cell death (apoptosis) by proinflammatory cytokines such as TNF-alpha, interleukin(IL)-1, and high concentrations of Ox-LDL occurs via activation of a cell membrane-associated N-SMase (Arterioscler. Thromb. Vasc. Biol. 1998, 18(10) : 1523-33). Moreover, an antibody against N-SMase can abrogate Ox-LDL and TNF-alpha induced apoptosis. Overexpression of recombinant human N-SMase in human aortic smooth muscle cells markedly stimulates apoptosis. Since plaque stability is an integral aspect of atherosclerosis management, activation of N-SMase and subsequent apoptosis may be vital events in the onset of plaque rupture, stroke and heart failure (Chem. Phys. Lipids 1999, 102(1-2) : 79-96).

Lung epithelium plays a significant role in modulating the inflammatory response to lung injury. Exposure of human airway epithelial cells to H_2O_2 induces a greater than 2-fold activation of N-SMase activity with concomitant sphingomyelin hydrolysis, ceramide generation, and apoptosis (Am. J. Respir. Cell Mol. Biol. 2000, 22(4) : 460-8).

The antigen-specific signal mediated by the T-cell receptor (TCR) is essential for activation of T-cells; however, additional co-stimulatory signals are required for complete T-cell activation. Ligation of CD28 initiated sphingomyelin hydrolysis and generated ceramide. Treatment of T cells with either exogenous SMase or a cell-permeable ceramide analogue, C6-ceramide, mimicked the CD28 signal by inducing T cell proliferation and IL-2 gene transcription (Eur. J. Immunol. 1995, 25(7) : 1999-2004). Inhibition of ceramide production by

fumonisin B1 impaired TCR-induced IL-2 production and programmed cell death. Moreover, specific inactivation of N-SMase by antisense RNA inhibited IL-2 production and mitogen-activated protein kinase activation after TCR triggering. These results suggest that ceramide production by activation of N-SMase is an essential component of the TCR signaling machinery (J. Exp. Med. 1999, 189(10) : 1581-9). Blocking strategies of co-stimulatory signals have been evaluated as targets of therapeutic intervention for graft versus host disease (Ann. Hematol. 2000 Jun; 79(6) : 83-90). Moreover, the potential for the inhibition of these co-stimulatory pathways has been reported to induce transplantation tolerance (J. Am. Soc. Nephrol. 1999, 10(6) : 1356-65).

Renal injury dramatically increases total ceramide by approximately 300% (Am. J. Physiol. 1999, 277(5 Pt 2) : F723-33). Synthetic cell permeable C2-ceramide induced apoptotic death of rat neonatal cardiomyocytes in vitro. In the rat heart left coronary artery occlusion model, the content of ceramide in ischemic area was significantly elevated (Am. J. Pathol. 1997, 151(5) : 1257-63). One of the earliest responses of cardiac myocytes to hypoxia and reoxygenation is the activation of N-SMase and accumulation of ceramide (Circ. Res. 2000, 86(2) : 198-204).

In the rat middle cerebral artery occlusion model, ceramide was produced in the cerebral cortex by the breakdown of sphingomyelin during early ischemia (Neurol. Res. 1996, 18(4) : 337-41). An increase of ceramide was found in the ischemic human brain of an acute case of internal carotid artery occlusion (Jpn. J. Exp. Med. 1989, 59(2) : 59-64).

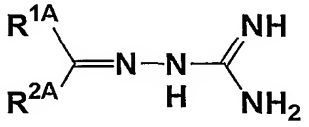
A drastic increase was observed in the ceramide levels after HIV-infection, whereas sphingosine levels were hardly influenced (Biochem. Biophys. Res. Commun. 1992, 187(1) : 209-16). Ceramide treatment resulted in a 20- to 100-fold enhancement of HIV production in infected myelomonocytic cells

(AIDS Res. Hum. Retroviruses 1994, 10(7) : 775-80).

N-SMase inhibitors are useful for the prevention and / or treatment of various diseases induced by activation of N-SMase. Such diseases are, for example, arteriosclerosis, cerebral ischemia, cardiac ischemia, lung injury, renal injury, GVHD (graft versus host diseases), transplant rejection, HIV etc.

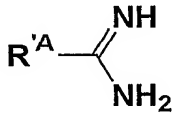
Related arts

Some sphingomyelinase inhibitors are known. For example, in the specification of WO 9745401, pharmaceuticals containing at least one compound of formula (I^A)



(I^A)

and/or (II^A)

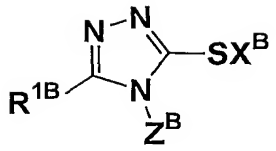


(II^A)

(wherein R'^A and R^{1A} are adamantyl, norbornyl, tricyclodecyl, benzyl, furyl, pyridyl, indolyl, quinolyl, phenyl, anthracenyl, naphthyl, phenanthryl, perinaphthyl, quinuclidinyl, 3-20C alkyl (optionally substituted by OH, NH_2, halo, 1-4C alkoxy) or 3-20C cycloalkyl (optionally substituted by OH, NH_2, halo, 1-4C alkoxy or 1-4C alkyl, etc.); and, R^{2A} is H or as for R^{1A}) are disclosed as sphingomyelinase inhibitors, useful for the treatment for viral, inflammatory and auto-immune diseases and tumors.

On the other hand, the following thio-substituted triazoline derivative is known.

In the specification of JP Kokai 5-124947 (none corresponding EP or US patent), it is disclosed that a compound of formula (IB)



(I^B)

wherein X^B is H, alkali (ne earth) metal, ammonium or organic amine residue; R^{1B} is H, 1-22C alkyl, cycloalkyl, optionally substituted aralkyl, optionally substituted phenyl, etc., $NR^BR'^B$, Z^B is H, 1-22C alkyl, cycloalkyl, etc., is useful for the prophylaxis and treatment of chloasma caused by external stimuli such as UV as well as chloasma caused by pigment maculae such as endogenous chloasma, senile and solar lentigo, hormone abnormalities and internal organ disorders (necessary part is extracted in the explanation of the group).

But no sphingomyelinase inhibitors of 4H-1,2,4-triazole-3(2H)-thione derivatives were known so far.

Also, the following compounds are known:

1) 5-benzyl-4-phenyl-4H-1,2,4-triazole-3(2H)-thione,

2) 5-(5-chloro-2-hydroxyphenyl)-4-phenyl-4H-1,2,4-triazole-3(2H)-thione,

3) 5-(1-(2-phenylphenoxy)ethyl)-4-phenyl-4H-1,2,4-triazole-3(2H)-thione,

4) 5-(1-(4-chlorophenoxy)ethyl)-4-ethyl-4H-1,2,4-triazole-3(2H)-thione,

5) 5-(4-chloro-2-methylphenoxymethyl)-4-(2-propenyl)-4H-1,2,4-triazole-3(2H)-thione,

6) 5-(5-chloro-2-hydroxyphenyl)-4-methyl-4H-1,2,4-triazole-3(2H)-thione,

7) 5-(4-trifluoromethyloxyphenoxylmethyl)-4-(1-methylethyl)-4H-1,2,4-triazole-3(2H)-thione,

8) 5-(4-trifluoromethyloxyphenoxylmethyl)-4-(4-chlorophenyl)-4H-1,2,4-triazole-3(2H)-thione,

9) 5-(2-chlorophenyl)-4-phenyl-4H-1,2,4-triazole-3(2H)-thione,

10) 5-(4-bromophenoxymethyl)-4-phenyl-4H-1,2,4-triazole-

3(2H)-thione,

11) 5-(4-bromo-3,5-dimethylphenoxymethyl)-4-phenyl-4H-1,2,4-triazole-3(2H)-thione,

12) 5-(4-chloro-2-methylphenoxymethyl)-4-phenyl-4H-1,2,4-triazole-3(2H)-thione,

13) 5-(indol-3-ylmethyl)-4-phenyl-4H-1,2,4-triazole-3(2H)-thione,

14) 5-(2,3-dichlorophenoxymethyl)-4-phenyl-4H-1,2,4-triazole-3(2H)-thione,

15) 5-(2,4-dimethylphenoxymethyl)-4-phenyl-4H-1,2,4-triazole-3(2H)-thione,

16) 5-(3,4,5-trimethoxyphenyloxymethyl)-4-phenyl-4H-1,2,4-triazole-3(2H)-thione,

17) 5-(1-(4-chlorophenylthio)ethyl)-4-phenyl-4H-1,2,4-triazole-3(2H)-thione,

18) 5-(pyridin-4-yl)-4-(3-methyl-4-(1-methylethyl)phenyl)-4H-1,2,4-triazole-3(2H)-thione,

19) 5-(6-bromonaphthalen-2-yloxymethyl)-4-phenyl-4H-1,2,4-triazole-3(2H)-thione,

20) 5-(2-chloro-5-methylphenyloxymethyl)-4-phenyl-4H-1,2,4-triazole-3(2H)-thione,

21) 5-(3,5-bis(trifluoromethyl)phenyl)-4H-1,2,4-triazole-3(2H)-thione,

22) 5-(4-t-butylphenyl)-4H-1,2,4-triazole-3(2H)-thione,

23) 5-phenyl-4H-1,2,4-triazole-3(2H)-thione,

24) 5-(thiophen-2-yl)-4-phenyl-4H-1,2,4-triazole-3(2H)-thione,

25) 5-(2,3,4,5,6-tetramethylphenylmethylthiomethyl)-4-(4-fluorophenyl)-4H-1,2,4-triazole-3(2H)-thione,

26) 5-(2-chlorophenyl)-4-(2-methylphenyl)-4H-1,2,4-triazole-3(2H)-thione,

27) 5-(furan-2-yl)-4-(2-chlorophenyl)-4H-1,2,4-triazole-3(2H)-thione,

28) 5-(furan-2-yl)-4-(4-methoxyphenyl)-4H-1,2,4-triazole-

3(2H)-thione,

29) 5-(3,4,5-trimethoxyphenyl)-4-(4-methoxyphenyl)-4H-1,2,4-triazole-3(2H)-thione,

30) 5-(furan-2-yl)-4-(4-chlorophenyl)-4H-1,2,4-triazole-3(2H)-thione,

31) 5-(furan-2-yl)-4-phenyl-4H-1,2,4-triazole-3(2H)-thione,

32) 5-phenylamino-4-phenyl-4H-1,2,4-triazole-3(2H)-thione,

33) 5-(2-bromophenylamino)-4-(2-bromophenyl)-4H-1,2,4-triazole-3(2H)-thione,

34) 5-phenylamino-4-phenyl-2-hydroxymethyl-4H-1,2,4-triazole-3(2H)-thione).

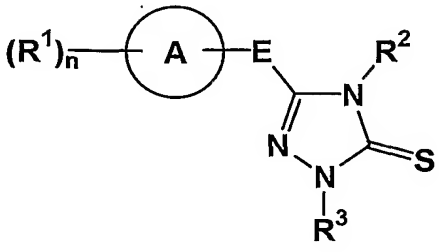
DISCLOSURE OF THE INVENTION

Energetic investigations have been carried out to discover a neutral sphingomyelinase inhibitor. As a result, the present inventors have found that 4H-1,2,4-triazole-3(2H)-thione derivatives of formula (I) have inhibitory activity against neutral sphingomyelinase, and have accomplished the present invention.

4H-1,2,4-Triazole-3(2H)-thione derivatives of formula (I) of the present invention are not known as neutral sphingomyelinase inhibitors at all. Novel 4H-1,2,4-triazole-3(2H)-thione derivatives of formula (Ia) of the present invention are not known at all.

The present invention relates to

1) a sphingomyelinase inhibitor comprising a 4H-1,2,4-triazole-3(2H)-thione derivative of formula (I)



(I)

wherein R^1 is C1-6 alkyl, C1-6 alkoxy, phenyl, hydroxy, amino, halogen, trifluoromethyl or trifluoromethyloxy;

A is a C3-10 mono- or bi-cyclic carbon ring or a 4-10 membered mono- or bi-cyclic hetero ring containing 1-3 of nitrogen, oxygen and/or sulfur,

E is a bond, C1-6 alkylene (one of carbon atom may be replaced by oxygen or sulfur, with the proviso that the carbon atom attached to triazoline ring is not replaced) or $-NR^4-$,

R^2 is hydrogen, C1-6 alkyl, C2-6 alkenyl, C2-6 alkynyl or C1-6 alkyl substituted by 1-3 of C3-10 mono- or bi-cyclic carbon ring or 4-10 membered hetero ring containing 1-3 of nitrogen, oxygen and/or sulfur,

Said carbon ring or hetero ring in R^2 may be substituted by C1-6 alkyl, C1-6 alkoxy, $SO_2NR^6R^7$, C2-6 acyl or halogen;

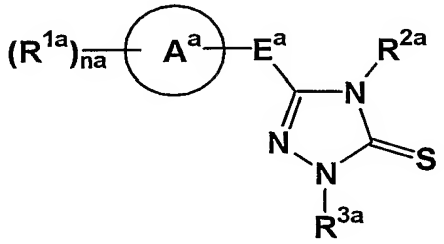
R^3 is hydrogen or C1-4 hydroxyalkyl;

n=0~5;

R^4 is hydrogen or C1-4 alkyl;

R^5 and R^6 are the same or different to represent hydrogen or C1-4 alkyl or R^5 and R^6 are taken together to form C3-6 alkylene,

2) a novel 4H-1,2,4-triazole-3(2H)-thione derivative of formula (Ia)



(Ia)

wherein R^{1a} is C1-6 alkyl, C1-6 alkoxy, phenyl, hydroxy, amino, halogen, trifluoromethyl or trifluoromethyloxy;

A^a is a C3-10 mono- or bi-cyclic carbon ring or a 4-10 membered mono- or bi-cyclic hetero ring containing 1-3 of nitrogen, oxygen and/or sulfur atom(s),

E^a is a bond, C1-6 alkylene (one of carbon atom may be replaced by oxygen or sulfur atom, with the proviso that the carbon atom attached to triazoline ring is not replaced) or $-NR^4-$,

R^{2a} is hydrogen, C1-6 alkyl, C2-6 alkenyl, C2-6 alkynyl, C1-6 alkyl substituted by 1-3 of C3-10 mono- or bi-cyclic carbon ring or 4-10 membered hetero ring containing 1-3 of nitrogen, oxygen and/or sulfur atom(s),

Said carbon ring or hetero ring in R^{2a} may be substituted by C1-6 alkyl, C1-6 alkoxy, $SO_2NR^{6a}R^{7a}$ or C2-6 acyl or halogen;

R^{3a} is hydrogen or C1-4 hydroxyalkyl;

n^a is 0 or an integer of 1 ~ 5;

R^{4a} is hydrogen or C1-4 alkyl;

R^{5a} and R^{6a} are the same or different to represent hydrogen, C1-4 alkyl, or R^{5a} and R^{6a} are taken together to form C3-6 alkylene), with the proviso that the following compounds (i) ~ (xxxiv) are excluded

(i) 5-benzyl-4-phenyl-4H-1,2,4-triazole-3(2H)-thione,

(ii) 5-(5-chloro-2-hydroxyphenyl)-4-phenyl-4H-1,2,4-triazole-3(2H)-thione,

(iii) 5-(1-(2-phenylphenoxy)ethyl)-4-phenyl-4H-1,2,4-triazole-3(2H)-thione,

(iv) 5-(1-(4-chlorophenoxy)ethyl)-4-ethyl-4H-1,2,4-triazole-3(2H)-thione,

(v) 5-(1-(4-chloro-2-methylphenoxy)ethyl)-4-(2-propenyl)-4H-1,2,4-triazole-3(2H)-thione,

(vi) 5-(5-chloro-2-hydroxyphenyl)-4-methyl-4H-1,2,4-triazole-3(2H)-thione,

(vii) 5-(4-trifluoromethyloxyphenoxylmethyl)-4-(1-methylethyl)-4H-1,2,4-triazole-3(2H)-thione,

(viii) 5-(4-trifluoromethyloxyphenoxylmethyl)-4-(4-chlorophenyl)-4H-1,2,4-triazole-3(2H)-thione,

(ix) 5-(2-chlorophenyl)-4-phenyl-4H-1,2,4-triazole-3(2H)-thione,

(x) 5-(4-bromophenoxymethyl)-4-phenyl-4H-1,2,4-triazole-3(2H)-thione,

(xi) 5-(4-bromo-3,5-dimethylphenoxymethyl)-4-phenyl-4H-1,2,4-triazole-3(2H)-thione,

(xii) 5-(4-chloro-2-methylphenoxymethyl)-4-phenyl-4H-1,2,4-triazole-3(2H)-thione,

(xiii) 5-(indol-3-ylmethyl)-4-phenyl-4H-1,2,4-triazole-3(2H)-thione,

(xiv) 5-(2,3-dichlorophenoxymethyl)-4-phenyl-4H-1,2,4-triazole-3(2H)-thione,

(xv) 5-(2,4-dimethylphenoxymethyl)-4-phenyl-4H-1,2,4-triazole-3(2H)-thione,

(xvi) 5-(3,4,5-trimethoxyphenyloxymethyl)-4-phenyl-4H-1,2,4-triazole-3(2H)-thione,

(xvii) 5-(1-(4-chlorophenylthio)ethyl)-4-phenyl-4H-1,2,4-triazole-3(2H)-thione,

(xviii) 5-(pyridin-4-yl)-4-(3-methyl-4-(1-methylethyl)phenyl)-4H-1,2,4-triazole-3(2H)-thione,

(xix) 5-(6-bromonaphthalen-2-yloxymethyl)-4-phenyl-4H-1,2,4-triazole-3(2H)-thione,

(xx) 5-(2-chloro-5-methylphenyloxymethyl)-4-phenyl-4H-1,2,4-triazole-3(2H)-thione,

(xxi) 5-(3,5-bis(trifluoromethyl)phenyl)- 4H-1,2,4-triazole-3(2H)-thione,

(xxii) 5-(4-t-butylphenyl)-4H-1,2,4-triazole-3(2H)-thione,

(xxiii) 5-phenyl-4H-1,2,4-triazole-3(2H)-thione,

(xxiv) 5-(thiophen-2-yl)-4-phenyl-4H-1,2,4-triazole-3(2H)-thione,

(xxv) 5-(2,3,4,5,6-tetramethylphenylmethylthiomethyl)-4-(4-fluorophenyl)-4H-1,2,4-triazole-3(2H)-thione,

(xxvi) 5-(2-chlorophenyl)-4-(2-methylphenyl)-4H-1,2,4-triazole-3(2H)-thione,

(xxvii) 5-(furan-2-yl)-4-(2-chlorophenyl)-4H-1,2,4-triazole-3(2H)-thione,

(xxviii) 5-(furan-2-yl)-4-(4-methoxyphenyl)-4H-1,2,4-triazole-3(2H)-thione,

(xxix) 5-(3,4,5-trimethoxyphenyl)-4-(4-methoxyphenyl)-

4H-1,2,4-triazole-3(2H)-thione,

(xxx) 5-(furan-2-yl)-4-(4-chlorophenyl)-4H-1,2,4-triazole-3(2H)-thione,

(xxxi) 5-(furan-2-yl)-4-phenyl-4H-1,2,4-triazole-3(2H)-thione,

(xxxii) 5-phenylamino-4-phenyl-4H-1,2,4-triazole-3(2H)-thione,

(xxxiii) 5-(2-bromophenylamino)-4-(2-bromophenyl)-4H-1,2,4-triazole-3(2H)-thione,

(xxxiv) 5-phenylamino-4-phenyl-2-hydroxymethyl-4H-1,2,4-triazole-3(2H)-thione,

and

3) a process for the preparation of the compounds of formula (Ia), non-toxic salts thereof and hydrates thereof.

DETAILED DESCRIPTION OF INVENTION

The present invention as above summarized is described in detail below.

In the formulae (I) and (Ia), C1-6 alkyl is methyl, ethyl, propyl, butyl, pentyl, hexyl and isomers thereof.

In the formulae (I) and (Ia), C2-6 alkenyl is vinyl (ethenyl), propenyl, butenyl, pentenyl, hexenyl and isomers thereof.

In the formulae (I) and (Ia), C2-6 alkynyl is ethynyl, propynyl, butynyl, pentynyl, hexynyl and isomers thereof.

In the formulae (I) and (Ia), C1-6 alkoxy is methoxy, ethoxy, propyloxy, butyloxy, pentyloxy, hexyloxy and isomers thereof.

In the formulae (I) and (Ia), halogen is fluorine, chlorine, bromine and iodine.

In the formulae (I) and (Ia), C2-6 acyl is acetyl, propionyl, butyryl, valeryl, hexanoyl and isomers thereof.

In the formulae (I) and (Ia), C1-4 alkyl is methyl, ethyl, propyl, butyl and isomers thereof.

In the formulae (I) and (Ia), C3-6 alkylene represented

by R^6 and R^7 is propylene, butylene, pentylene, hexylene.

In the formulae (I) and (Ia), C1-4 hydroxyalkyl is hydroxymethyl, hydroxyethyl, hydroxypropyl, hydroxybutyl and isomers thereof.

In the formulae (I) and (Ia), C3-10 mono- or bi-cyclic carbon ring includes, for example, cyclopropane, cyclobutane, cyclopentane, cyclohexane, cycloheptane, cyclooctane, cyclononane, cyclodecane, cyclopentene, cyclohexene, cyclopentadiene, cyclohexadiene, benzene, pentalene, indene, naphthalene, azulene, perhydronaphthalene, indane (dihydroindene), perhydroindene, dihydronaphthalene, tetrahydronaphthalene, perhydronaphthalene, perhydroazulene, etc.

In the formulae (I) and (Ia), hetero ring includes a 4~10 membered mono- or bi-cyclic hetero aryl, or partially or completely saturated one including 1~3 of nitrogen, oxygen and/or sulfur.

Said 4~10 membered mono- or bi-cyclic hetero aryl containing 1~3 of nitrogen, oxygen and/or sulfur includes pyrrole, imidazole, triazole, tetrazole, pyrazole, pyridine, pyrazine, pyrimidine, pyridazine, azepine, diazepine, furan, pyran, oxepin, thiophene, thiain (thiopyran), thiepin, oxazole, isoxazole, thiazole, isothiazole, oxadiazole, oxazine, ozadiazine, oxazepine, oxadiazepine, thiadiazole, thiazine, thiadiazine, thiazepine, thiadiazepine, indole, isoindole, benzofuran, isobenzofuran, benzothiophene, isobenzothiophene, indazole, quinoline, isoquinoline, phthalazine, naphthyridine, quinoxaline, quinazoline, cinnoline, benzoxazole, benzothiazole, benzoimidazole, etc.

Said mono- or bi-cyclic 4~10 membered hetero aryl, or partially or completely saturated one containing 1~3 of hetero atom(s) selected from nitrogen, oxygen or sulfur includes pyrroline, pyrrolidine, imidazoline, imidazolidine, triazoline, triazolidine, tetrazoline, tetrazolidine, dihydropyridine,

dihydropyrazine, dihydropyrimidine, dihydropyridazine, piperidine, piperazine, tetrahydropyrimidine, tetrahydropyridazine, dihydrofuran, tetrahydrofuran, dihydropyran, tetrahydropyran, dihydrothiophene, tetrahydrothiophene, dihydrothiaine (dihydrothiopyran), tetrahydrothiaine (tetrahydrothiopyran), dihydroxazole, tetrahydroxazole, dihydroisoxazole, tetrahydroisoxazole, dihydrothiazole, tetrahydrothiazole, dihydroisothiazole, tetrahydroisothiazole, morpholine, thiomorpholine, indoline, isoindoline, dihydrobenzofuran, perhydrobenzofuran, dihydroisobenzofuran, perhydroisobenzofuran, dihydrobenzothiophene, perhydrobenzothiophene, dihydroisobenzothiophene, perhydrobenzothiophene, dihydroisobenzothiophene, perhydroisobenzothiophene, dihydroindazole, perhydroindazole, dihydroquinoline, tetrahydroquinoline, perhydroquinoline, dihydroisoquinoline, tetrahydroisoquinoline, perhydroisoquinoline, dihydrophthalazine, tetrahydrophthalazine, perhydrophthalazine, dihydronaphthyridine, tetrahydronaphthyridine, perhydronaphthyridine, dihydroquinoxaline, tetrahydroquinoxaline, perhydroquinoxaline, dihydroquinazoline, tetrahydroquinazoline, perhydroquinazoline, dihydrocinnoline, tetrahydrocinnoline, perhydrocinnoline, dihydrobenzoxazole, perhydrobenzoxazole, dihydrobenzothiazole, perhydrobenzothiazole, dihydrobenzimidazole, perhydrobenzimidazole, benzofurazane, benzothiadiazole, benzotriazole, 1,3-benzodioxole, 1,4-benzodioxole ring, etc.

In the formulae (I) and (Ia), R^1 is preferably, C1~4 alkyl, C1~4 alkoxy, hydroxy, halogen, trifluoromethyl or trifluoromethoxy.

In the formulae (I) and (Ia), A is preferably, a 4~10 membered carbocyclic ring or a hetero ring, more preferably benzene, thiophene, furan, pyridine, naphthalene or indole.

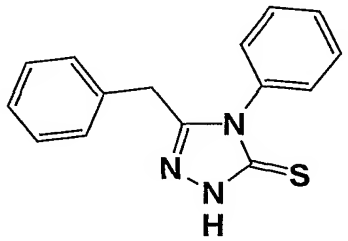
In the formulae (I) and (Ia), E is preferably a bond, C1-4 alkylene (one of the carbon atom may be replaced by oxygen or sulfur) or -NH-.

In the formulae (I) and (Ia), R^2 is preferably, C1~4 alkyl, C2~4 alkenyl, C1-4 alkyl substituted by C4~10 membered carbocyclic ring or 4~10 membered heterocyclic ring, a 4~10 membered carbocyclic ring or a 4~10 membered hetero ring. More preferably R^2 is methyl, ethyl, propyl, allyl, cyclohexylmethyl, phenyl, benzyl, thienyl, furyl, 1,3-benzodioxolyl.

In the formulae (I) and (Ia), R^3 is preferably, hydrogen or C1~2 alkyl substituted by hydroxy.

Preferable specific compounds of formulae (I) and (Ia) are the following compounds (1) ~ (34), and those described in the Examples.

Compound (1) 5-benzyl-4-phenyl-4H-1,2,4-triazole-3(2H)-thione (Maybridge Cat. No. JFD 00890)



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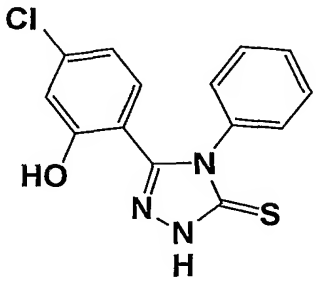
Compound (2) 5-(5-chloro-2-hydroxyphenyl)-4-phenyl-4H-1,2,4-triazole-3(2H)-thione (Maybridge Cat. No. NRB 00975)



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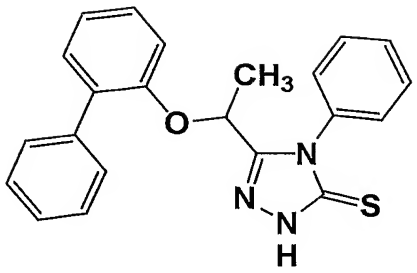
Compound (3) 5-(1-(2-phenylphenoxy)ethyl)-4-phenyl-4H-1,2,4-triazole-3(2H)-thione (Maybridge Cat. No. JFD 03210)



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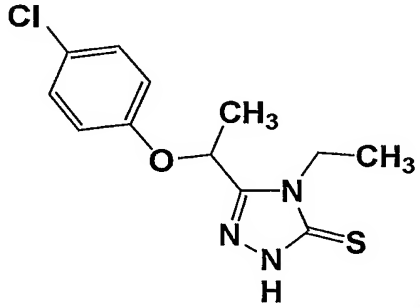
Compound (4) 5-(1-(4-chlorophenoxy)ethyl)-4-ethyl-4H-1,2,4-triazole-3(2H)-thione (Maybridge Cat. No. JFD 03212)



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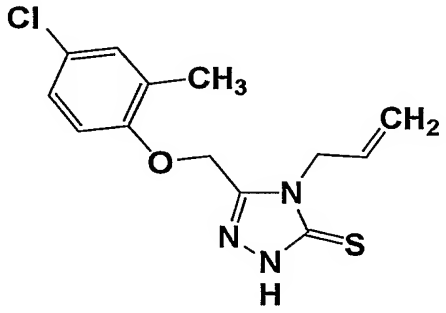
Compound (5) 5-(4-chloro-2-methylphenoxymethyl)-4-(2-propenyl)-4H-1,2,4-triazole-3(2H)-thione (Maybridge Cat. No. JFD 03204)



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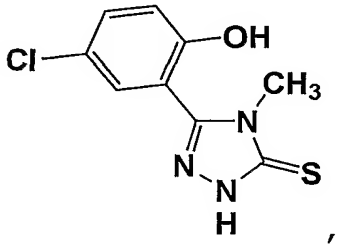
Compound (6) 5-(5-chloro-2-hydroxyphenyl)-4-methyl-4H-1,2,4-triazole-3(2H)-thione (Maybridge Cat. No. NRB 00994)



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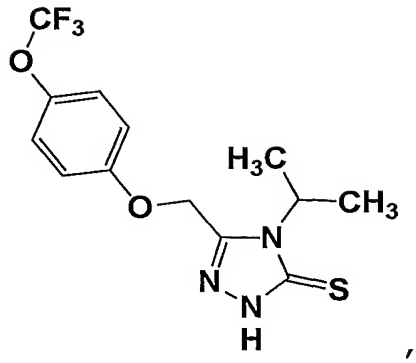
Compound (7) 5-(4-trifluoromethyloxyphenoxylmethyl)-4-(1-methylethyl)-4H-1,2,4-triazole-3(2H)-thione (Maybridge Cat. No. RDR 03526)



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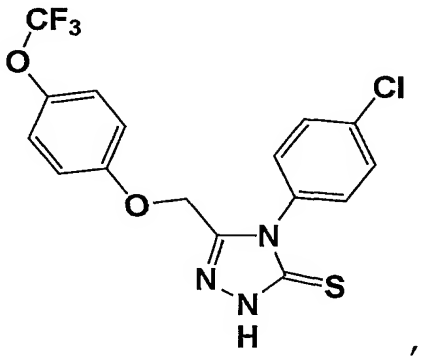
Compound (8) 5-(4-trifluoromethyloxyphenoxylmethyl)-4-(4-chlorophenyl)-4H-1,2,4-triazole-3(2H)-thione (Maybridge Cat. No. RDR 03520)



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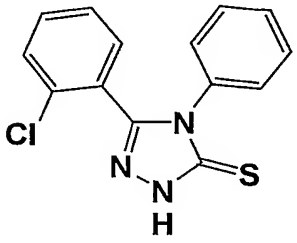
Compound (9) 5-(2-chlorophenyl)-4-phenyl-4H-1,2,4-triazole-3(2H)-thione (Menai Cat. No. DH61)



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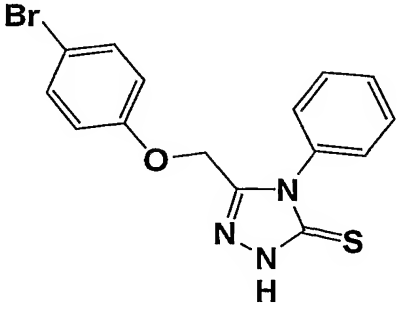
Compound (10) 5-(4-bromophenoxymethyl)-4-phenyl-4H-1,2,4-triazole-3(2H)-thione (Menai Cat. No. CB979)



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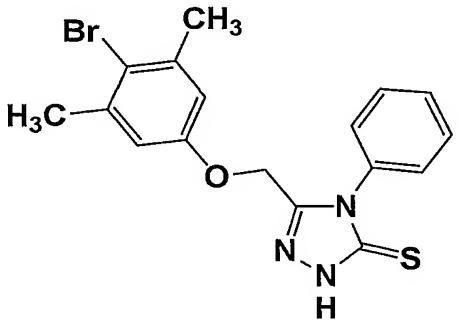
Compound (11) 5-(4-bromo-3,5-dimethylphenoxymethyl)-4-phenyl-4H-1,2,4-triazole-3(2H)-thione (Menai Cat. No. CB981)



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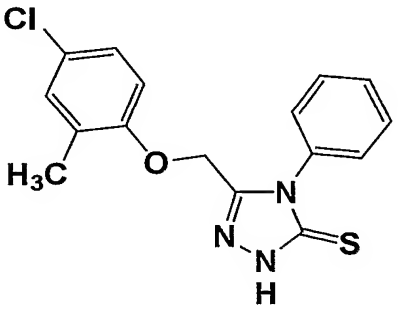
Compound (12) 5-(4-chloro-2-methylphenoxymethyl)-4-phenyl-4H-1,2,4-triazole-3(2H)-thione (Menai Cat. No. NC121)



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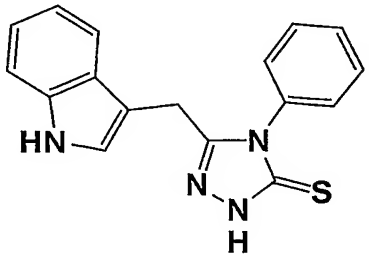
Compound (13) 5-(indol-3-ylmethyl)-4-phenyl-4H-1,2,4-triazole-3(2H)-thione (Menai Cat. No. SR32)



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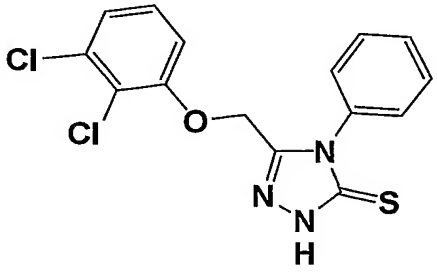
Compound (14) 5-(2,3-dichlorophenoxymethyl)-4-phenyl-4H-1,2,4-triazole-3(2H)-thione (Menai Cat. No. NC58)



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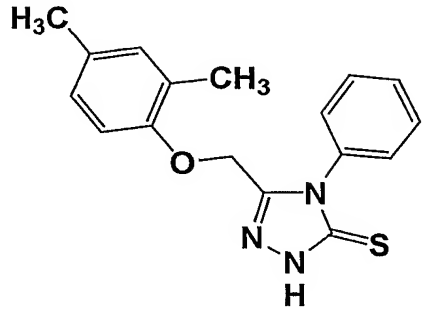
Compound (15) 5-(2,4-dimethylphenoxymethyl)-4-phenyl-4H-

1,2,4-triazole-3(2H)-thione (Menai Cat. No. SR323)



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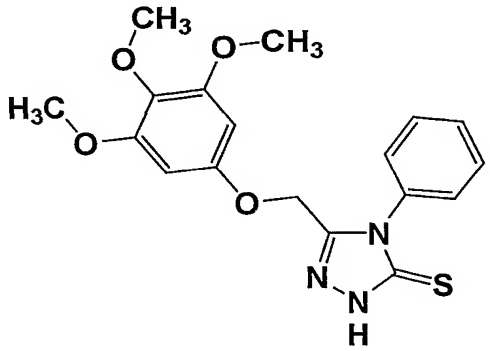
Compound (16) 5-(3,4,5-trimethoxyphenyloxymethyl)-4-phenyl-4H-1,2,4-triazole-3(2H)-thione (Menai Cat. No. NJ104)



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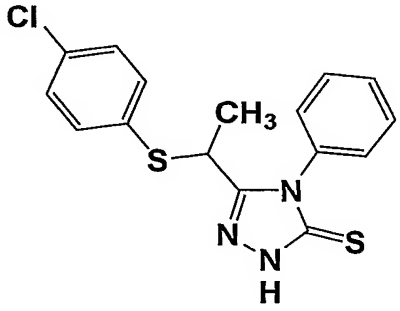
Compound (17) 5-(1-(4-chlorophenylthio)ethyl)-4-phenyl-4H-1,2,4-triazole-3(2H)-thione (Menai Cat. No. SR287)



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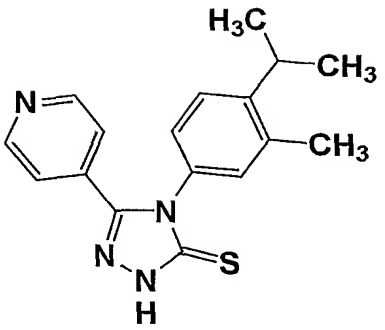
Compound (18) 5-(pyridin-4-yl)-4-(3-methyl-4-(1-methylethyl)phenyl)-4H-1,2,4-triazole-3(2H)-thione (Menai Cat. No. LJ413)



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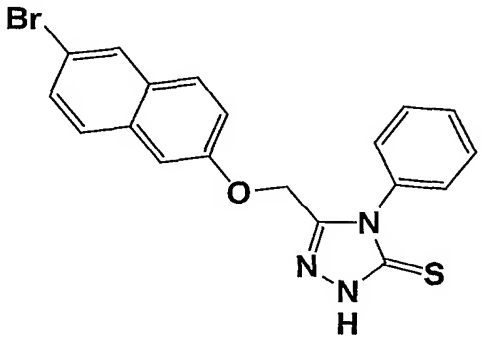
Compound (19) 5-(6-bromonaphthalen-2-yloxymethyl)-4-phenyl-4H-1,2,4-triazole-3(2H)-thione (Menai Cat. No. DW62)



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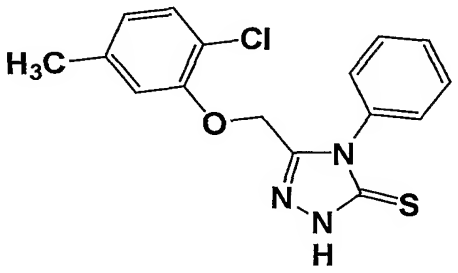
Compound (20) 5-(2-chloro-5-methylphenyloxymethyl)-4-phenyl-4H-1,2,4-triazole-3(2H)-thione (Menai Cat. No. DW75)



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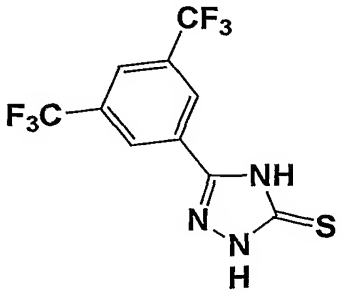
Compound (21) 5-(3,5-bis(trifluoromethyl)phenyl)-4H-1,2,4-triazole-3(2H)-thione (CAS REGISTRY No. 175276-77-4)



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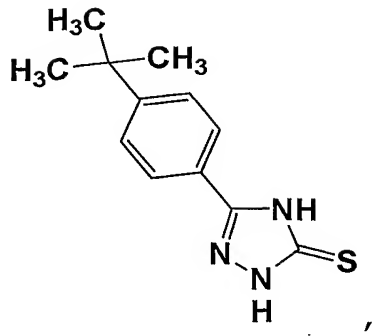
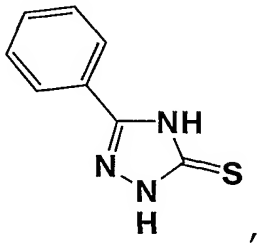
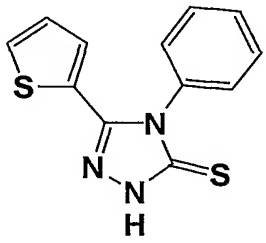
Compound (22) 5-(4-t-butylphenyl)-4H-1,2,4-triazole-3(2H)-thione (Maybridge Cat. No. 07-115)



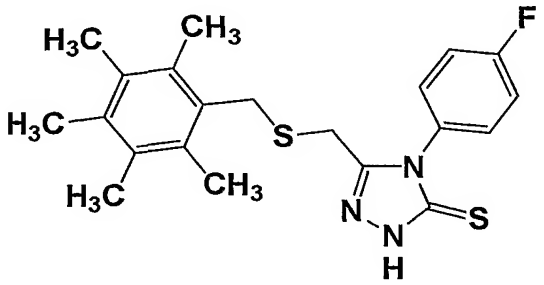
Compound (23) 5-phenyl-4H-1,2,4-triazole-3(2H)-thione (CAS Registry No. 3414-94-6)



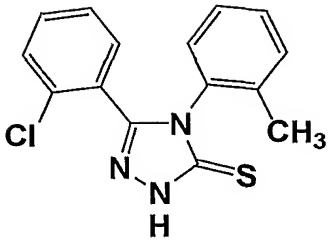
Compound (24) 5-(thiophen-2-yl)-4-phenyl-4H-1,2,4-triazole-3(2H)-thione (Menai Cat. No. CB1134)



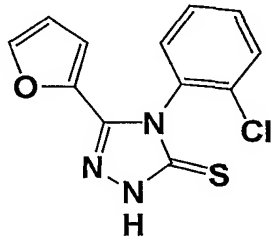
Compound (25) 5-(2,3,4,5,6-tetramethylphenylmethylthiomethyl)-4-(4-fluorophenyl)-4H-1,2,4-triazole-3(2H)-thione (Maybridge Cat. No. DSHS 00983)



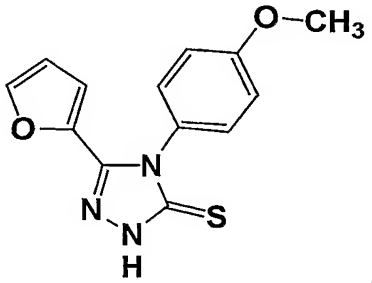
Compound (26) 5-(2-chlorophenyl)-4-(2-methylphenyl)-4H-1,2,4-triazole-3(2H)-thione (Maybridge Cat. No. BTB 01269)



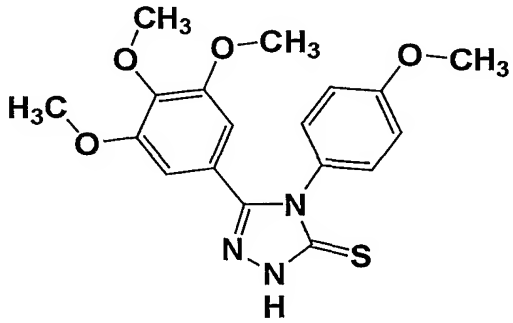
Compound (27) 5-(furan-2-yl)-4-(2-chlorophenyl)-4H-1,2,4-triazole-3(2H)-thione (Maybridge Cat. No. ML 00338)



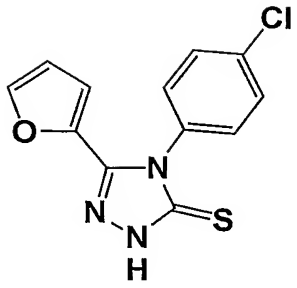
Compound (28) 5-(furan-2-yl)-4-(4-methoxyphenyl)-4H-1,2,4-triazole-3(2H)-thione (Maybridge Cat. No. ML 00345)



Compound (29) 5-(3,4,5-trimethoxyphenyl)-4-(4-methoxyphenyl)-4H-1,2,4-triazole-3(2H)-thione (Maybridge Cat. No. ML 00366)



Compound (30) 5-(furan-2-yl)-4-(4-chlorophenyl)-4H-1,2,4-triazole-3(2H)-thione (Maybridge Cat. No. JFD 00905)



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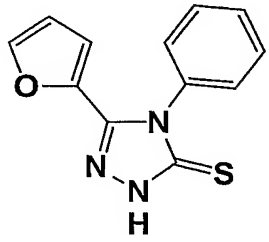
Compound (31) 5-(furan-2-yl)-4-phenyl-4H-1,2,4-triazole-3(2H)-thione (Maybridge Cat. No. JFD 00887)



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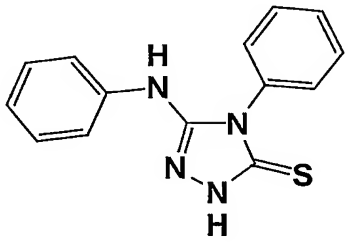
Compound (32) 5-phenylamino-4-phenyl-4H-1,2,4-triazole-3(2H)-thione (CAS Registry No. 14132-84-4)



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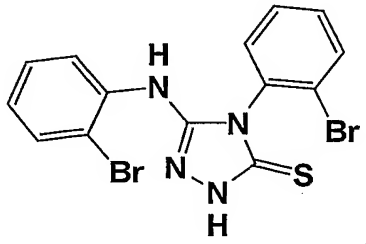
Compound (33) 5-(2-bromophenylamino)-4-(2-bromophenyl)-4H-1,2,4-triazole-3(2H)-thione (Aldrich Cat. No. S4014-3)



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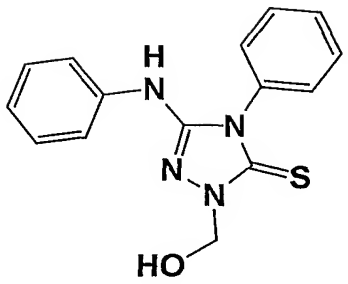
Compound (34) 5-phenylamino-4-phenyl-2-hydroxymethyl-4H-1,2,4-triazole-3(2H)-thione (Maybridge Cat. No. JFD 01890)



Isomers

Unless otherwise specified, all isomers are included in the present invention. For example, alkyl, alkenyl, alkynyl, alkoxy, alkylthio, alkylene, alkenylene and alkynylene include straight-chain and branched-chain ones. Moreover, the isomers in the structure of a double bond, ring, fused ring (E, Z, cis, trans), isomers generated by the presence of asymmetric carbon atom(s) etc. (R, S isomers, α, β isomers, enantiomers, diastereomers), optically active isomers having optical rotation (D, L, d, l isomers), isomers separated by chromatography (more polar or less polar isomers), equilibrium compounds, compounds of arbitrary ratio of these compounds are included in the present invention.

Salts

The compounds of formulae (I) and (Ia) of the present specification may be converted to corresponding salts by known methods. Non-toxic and water-soluble salts are preferable. Suitable salts include salts of alkali metal (potassium, sodium, etc.), salts of alkaline earth metal (calcium, magnesium, etc.), ammonium salts, pharmaceutically acceptable salts of organic amine (tetramethylammonium, triethylamine, methylamine, dimethylamine, cyclopentylamine, benzylamine, phenethylamine, piperidine, monoethanolamine, diethanolamine, tris(hydroxymethyl)aminomethane, lysine, arginine, N-methyl-D-glucamine, etc.).

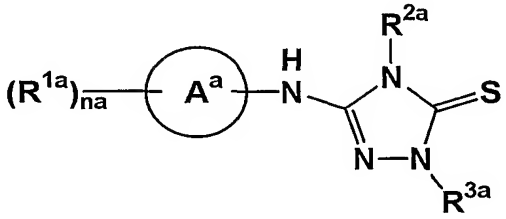
The compounds of formulae (I) and (Ia) of the present

invention may be converted to corresponding acid addition salts by known methods. Non-toxic and water-soluble acid addition salts are preferable. Suitable acid addition salts include salts of inorganic acid (e.g. salts of hydrochloric acid, hydrobromic acid, sulfuric acid, phosphoric acid, nitric acid) and salts of organic acid (e.g. salts of acetic acid, trifluoroacetic acid, lactic acid, tartaric acid, oxalic acid, fumaric acid, maleic acid, citric acid, benzoic acid, methanesulfonic acid, ethanesulfonic acid, benzenesulfonic acid, toluenesulfonic acid, isethionic acid, glucuronic acid and gluconic acid), etc.

The compounds of the formulae (I) and (Ia) of the present invention or salts thereof may be converted to hydrates by known methods.

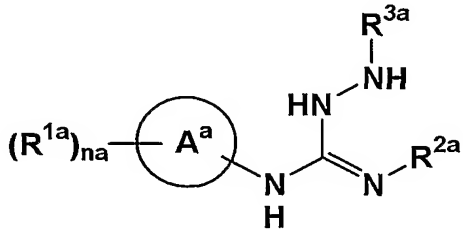
Process for the preparation

(i) Among the compounds of formula (Ia), wherein E^a is -NH-, i.e. a compound of formula (Ia-1)



(Ia-1)

wherein all symbols have the same meaning as hereinbefore described, may be prepared by subjecting to a reaction a compound of formula (II)



(II)

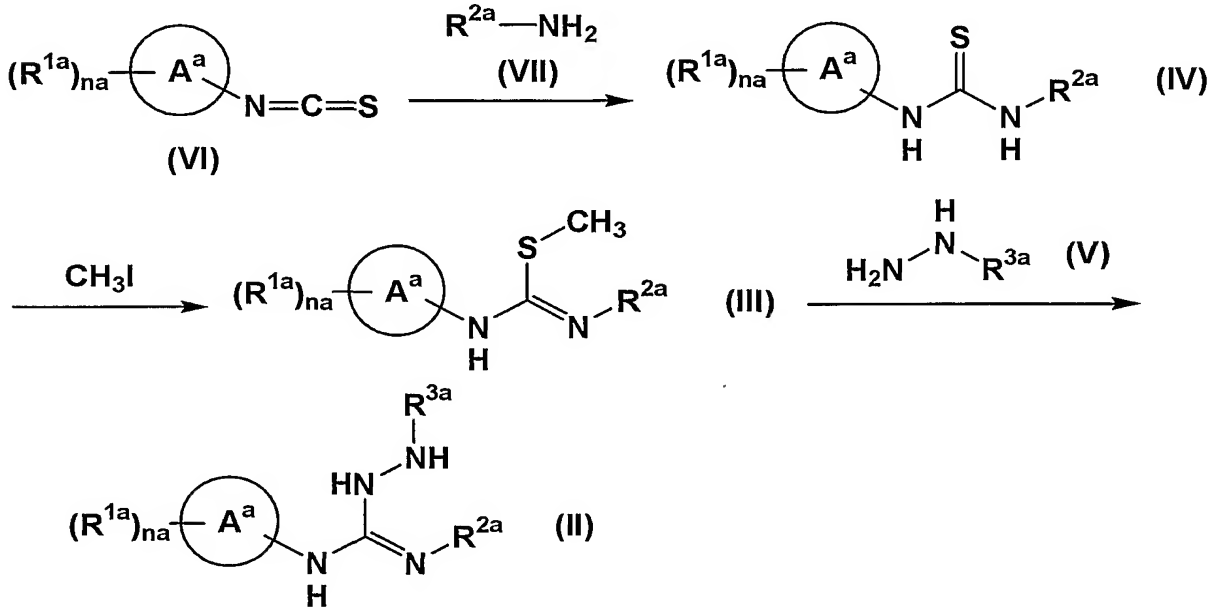
wherein all symbols are as described hereinbefore and carbon disulfide.

The reaction of a compound of formula (II) and carbon

disulfide is known, and for example, it is carried out in an organic solvent (dimethylformamide, dimethylacetamide, dimethylsulfoxide, etc.) at a temperature between 20℃ and 150℃.

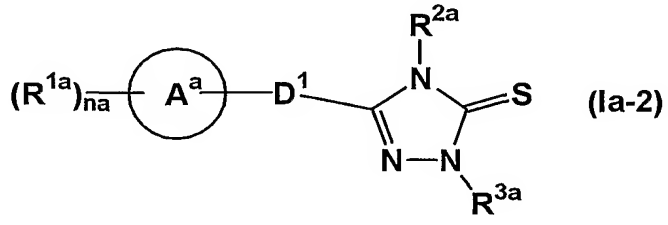
The compound of formula (II) may be prepared by the following scheme A.

Scheme A



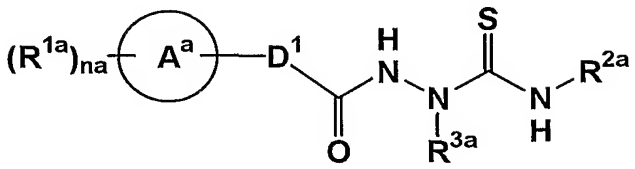
In the scheme A, all symbols are as hereinbefore described.

(ii) Among the compounds of formula (Ia), wherein E^a is a bond or C1-6 alkylene (one of carbon atom may be replaced by oxygen or sulfur, with the proviso that the carbon atom attached to triazoline ring is not replaced), i.e. a compound of formula (Ia-2)



wherein D^1 is a bond or C1-6 alkylene (one of carbon atom may be replaced by oxygen or sulfur, with the proviso that the carbon atom attached to triazoline ring is not replaced, and the other symbols are as hereinbefore described) may be prepared by

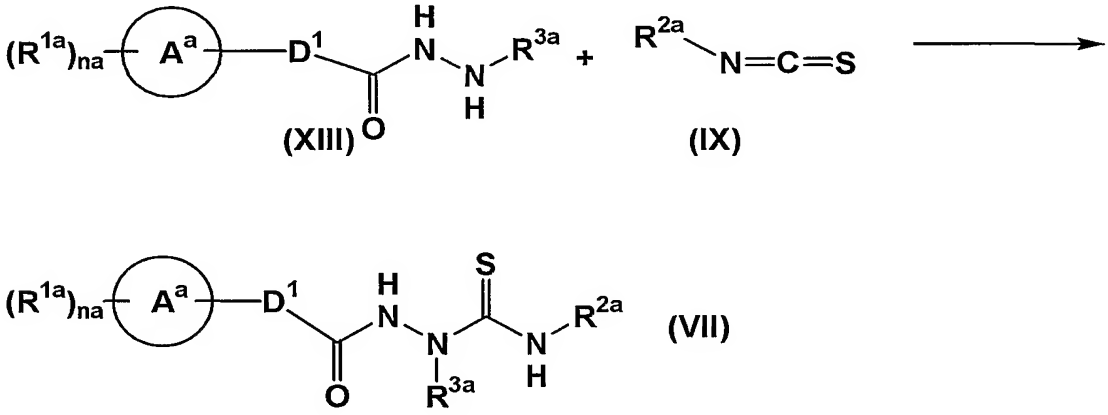
cyclizing a compound of formula (VII)



(VII)

wherein all symbols are as described hereinbefore. The cyclization reaction is known, and for example, it is carried out in an organic solvent (methanol, ethanol, tetrahydrofuran, dioxane, etc.) using hydroxide of alkali metal (sodium hydroxide, potassium hydroxide, lithium hydroxide, etc.), hydroxide of alkaline earth metal (barium hydroxide, calcium hydroxide, etc.) or carbonate (sodium carbonate, potassium carbonate, etc.) or an aqueous solution thereof or a mixture thereof at a temperature between 0 ℃ and refluxing temperature. The compound of formula (VII) is prepared by the following scheme B.

Scheme B



In the scheme B, all symbols are as hereinbefore described.

The starting materials in the reaction schemes are known per se or may be prepared by known methods.

The compounds of formulae (V), (VI), (VII), (XIII) and (XIV) are known per se or may be prepared by known methods easily.

The reactions of the reaction schemes may be carried out by known methods.

The other starting materials and reagents in the present invention are known per se or may be prepared by known methods.

In each reaction described in the present specification,

reaction products may be purified by conventional techniques. For example, purification may be carried out by distillation at atmospheric or reduced pressure, by high performance liquid chromatography, thin layer chromatography or column chromatography using silica gel or magnesium silicate, by washing or by recrystallization, etc. Purification may be carried out after each reaction, or after a series of reactions.

Pharmacological Activities

The inhibitory activity against neutral sphingomyelinase was confirmed as follows.

1) Inhibitory activity against neutral sphingomyelinase (in vitro)

Assays were conducted at 37°C in a total volume of 100μL. First, 50 μL of substrate solution (50μM [methyl-^{14}C]sphingomyelin in reaction buffer containing 20mM HEPES NaOH pH7.4, 20mM $MgCl_2$, and 0.1% Triton X-100) and 10μL of a solution of the compound of the present invention (DMSO solution) were mixed and preincubated for 5 min. Next, reactions were initiated by the addition of 40μL of enzyme solution (containing 1U of mouse neutral sphingomyelinase, 20mM HEPES NaOH pH7.4 solution), and subsequently terminated after 30min by the addition of 400μL of chloroform/methanol (1:1 v/v). After vortex mixing and centrifugation, the mass of hydrolysed [N-methyl-^{14}C]phosphorylcholine in the aqueous phase was determined by measuring of the ^{14}C radioactivity using a liquid scintillation counter.

Using serial logarithmic concentrations of the compound of the present invention as independent variables and corresponding inhibitory percentages as dependent variables, a linear regression analysis by the least squares method was carried out to calculate IC_{50} values.

The results are shown in Table 1 and 2.

Table 1

Compound No.	IC50 (μM)
(1)	3.8
(2)	3.3
(7)	4.8
(10)	3.7
(13)	3.2
(21)	4.3
(22)	3.5
(23)	4.1
(24)	4.6
(32)	3.1
(33)	4.1
(34)	2.5

Table 2

Examples No.	IC50 (μM)
1(2)	4.9
2	2.8
2 (6)	2.4

Inhibitory activities of the compound of the present invention on human neutral sphingomyelinase can also be determined by exchanging mouse neutral sphingomyelinase for human neutral sphingomyelinase.

2) Inhibitory activities of the compound of the present invention on IL-2 secretion in T cells can be measured as follows.

IL-2 secretion in Jurkat cells (cell based)

Jurkat cells (human T cell leukemia cell line, 4 x 10^5 cells/well) are incubated in 96-well tissue culture plate with the compound of the present invention for 1hr at 37 °C before stimulation with 4 μM Ionomycin, 40 nM Phorbol-myristate-acetate

and 4 μg/ml anti-CD28. After stimulation cells are incubated for 6hr at 37 °C and cell culture supernatants are analyzed with IL-2 ELISA.

Using serial logarithmic concentrations of the compound of the present invention as independent variables and corresponding inhibitory percentages as dependent variables, a linear regression analysis by the least squares method was carried out to calculate IC_{50} value.

Toxicity

The toxicity of the compounds of the present invention is very low and therefore they are considered to be safe enough for pharmaceutical use.

INDUSTRIAL APPLICABILITY

The compounds of the present invention of the formulae (I) and (Ia) are neutral sphingomyelinase inhibitors and therefore are useful for the treatment and/or prevention of arteriosclerosis, cerebral ischemia, cardiac ischemia, lung injury, renal injury, GVHD (graft versus host diseases), transplant rejection, HIV etc.

For the purposes described above, the compounds of the present invention of formulae (I) and (Ia), non-toxic salts, acid addition salts or hydrates thereof may be administered normally usually systemically or topically, orally or parenterally.

The doses to be administered are determined depending upon, for example, age, body weight, symptom, the desired therapeutic effect, the route of administration, and the duration of the treatment. In the human adult, the doses per person are generally in the range of from 1 mg to 1000 mg, by oral administration, up to several times per day, and in the range of from 0.1 mg to 100 mg, by parenteral administration (preferably intravenous administration), up to several times per day, or continuous administration from 1 to 24 hours per day from vein.

As mentioned above, the doses to be used depend upon various conditions. Therefore, there are cases in which doses lower than or greater than the ranges specified above may be used.

The compounds of the present invention may be administered in the form of, for example, solid forms for oral administration, liquid forms for oral administration, injections, liniments or suppositories for parenteral administration.

Solid forms for oral administration include compressed tablets, pills, capsules, dispersible powders, and granules, etc. Capsules include hard capsules and soft capsules.

In these solid forms, one or more of the active compound(s) may be admixed with excipients (e.g. lactose, mannitol, glucose, microcrystalline cellulose, starch), binders (e.g. hydroxypropyl cellulose, polyvinylpyrrolidone or magnesium metasilicate aluminate), disintegrants (e.g. cellulose calcium glycolate), lubricants (e.g. magnesium stearate), stabilizing agents, and adjuvants to assist dissolution (e.g. glutamic acid, aspartic acid) and prepared according to methods well known to those skilled in the art. The solid forms may, if desired, be coated with coating agents (e.g. sugar, gelatin, hydroxypropyl cellulose or hydroxypropylmethyl cellulose phthalate), or be coated with two or more films. Further, coating may include containment within capsules of absorbable materials such as gelatin.

Liquid forms for oral administration include pharmaceutically acceptable aqueous solutions, suspensions and emulsions, syrups and elixirs, etc. In such forms, one or more of the active compound(s) may be dissolved, suspended or emulsified into diluent(s) commonly used in the art (e.g. purified water, ethanol or a mixture thereof). Besides such liquid forms may also comprise wetting agents, suspending agents, emulsifying agents, sweetening agents, flavoring agents, aroma, preservative or buffering agent, etc.

Injections for parenteral administration include sterile aqueous, suspensions, emulsions and solid forms which are dissolved or suspended into solvent(s) for injection immediately before use. In injections, one or more of the active compound(s) may be dissolved, suspended or emulsified into solvent(s). The solvents may include distilled water for injection, physiological salt solution, vegetable oil, propylene glycol, polyethylene glycol, alcohol, e.g. ethanol, or a mixture thereof.

Injections may comprise some additives, such as stabilizing agents, solution adjuvants (e.g. glutamic acid, aspartic acid or POLYSORBATE80 (registered trademark)), suspending agents, emulsifying agents, soothing agent, buffering agents, preservatives. They may be sterilized at the final step, or may be prepared and compensated according to sterile methods. They may also be manufactured in the form of sterile solid forms, which may be dissolved in sterile water or some other sterile diluent(s) for injection immediately before use.

Other forms for parenteral administration include liquids for external use, ointments and endermic liniments, inhalations, sprays, suppositories and pessaries for vaginal administration which comprise one or more of the active compound(s) and may be prepared by methods known per se. Sprays may comprise additional substances other than diluents, such as stabilizing agents (e.g. sodium sulfate), isotonic buffers (e.g. sodium chloride, sodium citrate or citric acid). For preparation of such sprays, for example, the method described in the United States Patent No. 2,868,691 or 3,095,355 may be used.

BEST MODE FOR CARRYING OUT THE INVENTION

The following reference examples and examples illustrate the present invention, but do not limit the present invention.

Analytical LC / MS conditions:

HPLC Column : reverse phase C-18

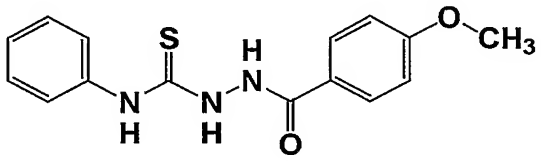
mobile phase : 10-90% acetonitrile in water over 3.7 min., water containing 0.05%

trifluoroacetic acid, acetonitrile containing 0.035% trifluoroacetic acid

flow rate : 3.5 ml / min

Reference Example 1

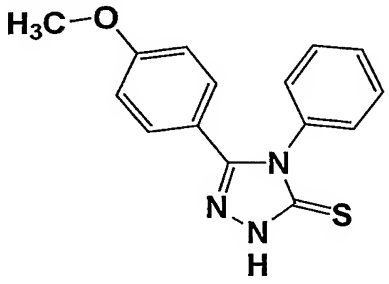
N'-phenylaminothiocarbonyl-(4-methoxybenzo)hydrazide



Phenylisothiocyanate (200 mg, 1.5 mmol) was dissolved in dry tetrahydrofuran (3.3 ml) and thereto was added a solution of 4-methoxybenzohydrazine (270 mg, 1.65 mmol) in tetrahydrofuran (5.4 ml). The resulting reaction mixture was stirred at 65 ℃ for two hours and at room temperature overnight. The solvent was removed under reduced pressure and the crude material (yield in mg not determined) was used in the next reaction.

Example 1

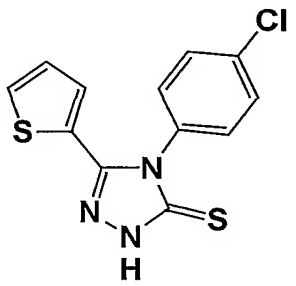
5-(4-methoxyphenyl)-4-phenyl-4H-1,2,4-triazole-3(2H)-thione



The crude compound prepared in Reference Example 1 (0.75 mmol crude) was suspended in a 2N aqueous solution of sodium hydroxide (2.5 ml) and heated to 100 ℃ for 3 hours. The solution

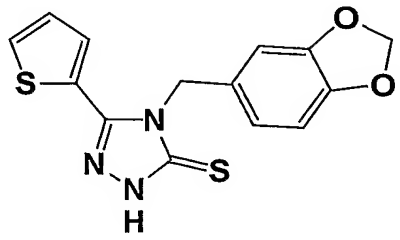
was allowed to cool and was acidified with dilute hydrochloric acid. The precipitate was filtered off and washed with water. The compounds were extracted with ethyl acetate, the organic layer was washed with water, dried over anhydrous magnesium sulfate and the mixture was concentrated under reduced pressure to yield the title compound having the following physical data.
Retention time (min.) : 3.13;
Mass (ESI, Pos) : m/z 284 $(M+H)^+$.

EXAMPLE 1 (1)
5-(thiophen-2-yl)-4-(4-chlorophenyl)-4H-1,2,4-triazole-3(2H)-thione



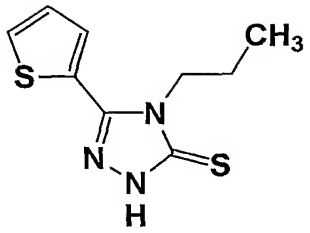
Retention time (min.): 3.38;
Mass (ESI, Pos) : m/z 294 $(M+H)^+$.

EXAMPLE 1 (2)
5-(thiophen-2-yl)-4-(1,3-benzodioxol-5-ylmethyl)-4H-1,2,4-triazole-3(2H)-thione



Retention time (min.): 3.28;
Mass (ESI, Pos) : m/z 318 $(M+H)^+$.

EXAMPLE 1 (3)
5-(thiophen-2-yl)-4-propyl-4H-1,2,4-triazole-3(2H)-thione

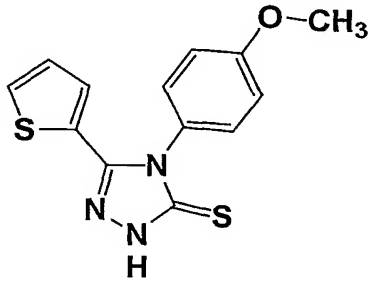


Retention time (min.): 2.97;

Mass (ESI, Pos) : m/z 226 $(M+H)^+$.

EXAMPLE 1 (4)

5-(thiophen-2-yl)-4-(4-methoxyphenyl)-4H-1,2,4-triazole-3(2H)-thione

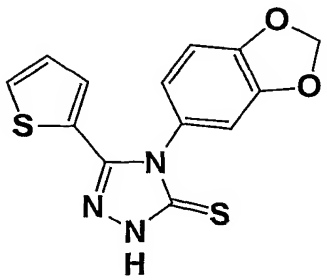


Retention time (min.): 3.13;

Mass (ESI, Pos) : m/z 290 $(M+H)^+$.

EXAMPLE 1 (5)

5-(thiophen-2-yl)-4-(1,3-benzodioxol-5-yl)-4H-1,2,4-triazole-3(2H)-thione



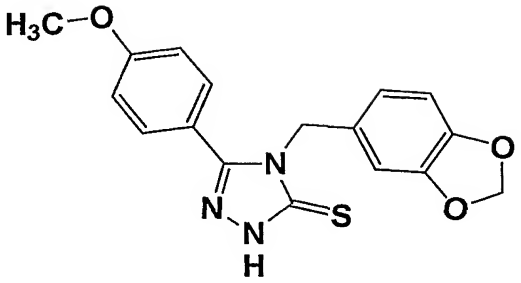
Retention time (min.): 3.04;

Mass (ESI, Pos) : m/z 304 $(M+H)^+$.

EXAMPLE 1 (6)

5-(4-methoxyphenyl)-4-(1,3-benzodioxol-5-ylmethyl)-4H-1,2,4-

triazole-3(2H)-thione

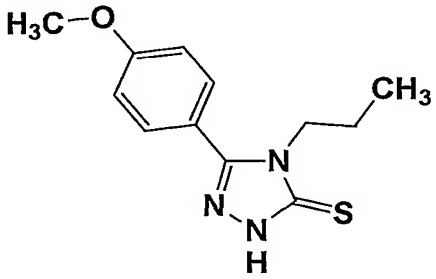


Retention time (min.) : 3.37;

Mass (ESI, Pos) : m/z 342 $(M+H)^+$.

EXAMPLE 1 (7)

5-(4-methoxyphenyl)-4-propyl-4H-1,2,4-triazole-3(2H)-thione

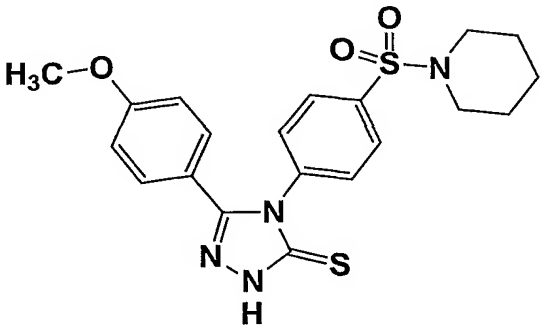


Retention time (min.) : 3.1;

Mass (ESI, Pos) : m/z 250 $(M+H)^+$.

EXAMPLE 1 (8)

5-(4-methoxyphenyl)-4-(4-piperidinosulfonylphenyl)-4H-1,2,4-triazole-3(2H)-thione

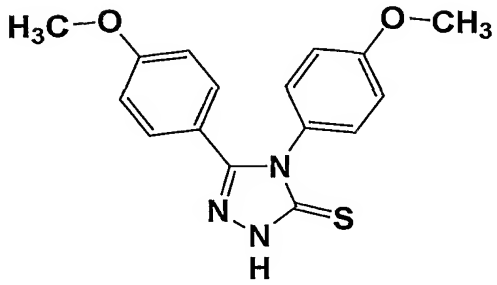


Retention time (min.) : 3.53;

Mass (ESI, Pos) : m/z 431 $(M+H)^+$.

EXAMPLE 1 (9)

5-(4-methoxyphenyl)-4-(4-methoxyphenyl)-4H-1,2,4-triazole-3(2H)-thione

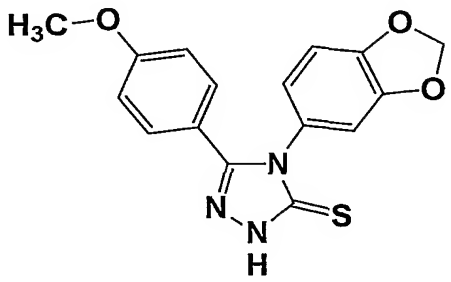


Retention time (min.) : 3.2;

Mass (ESI, Pos) : m/z 314 $(M+H)^+$.

EXAMPLE 1 (10)

5-(4-methoxyphenyl)-4-(1,3-benzodioxol-5-yl)-4H-1,2,4-triazole-3(2H)-thione

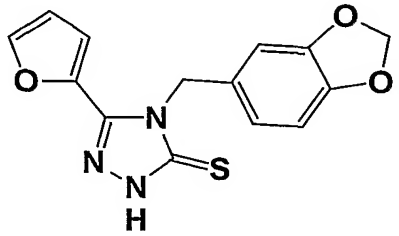


Retention time (min.) : 3.13;

Mass (ESI, Pos) : m/z 329 $(M+H)^+$.

EXAMPLE 1 (11)

5-(furan-2-yl)-4-(1,3-benzodioxol-5-ylmethyl)-4H-1,2,4-triazole-3(2H)-thione

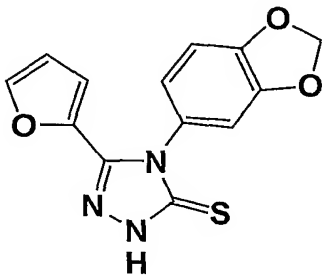


Retention time (min.) : 3.13;

Mass (ESI, Pos) : m/z 302 $(M+H)^+$.

EXAMPLE 1 (12)

5-(furan-2-yl)-4-(1,3-benzodioxol-5-yl)-4H-1,2,4-triazole-3(2H)-thione

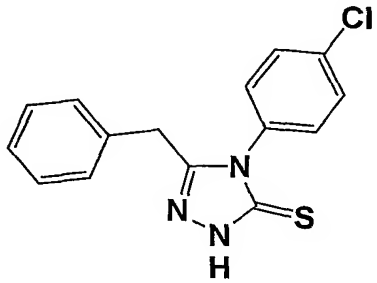


Retention time (min.) : 2.79;

Mass (ESI, Pos) : m/z 288 $(M+H)^+$.

EXAMPLE 1 (13)

5-benzyl-4-(4-chlorophenyl)-4H-1,2,4-triazole-3(2H)-thione

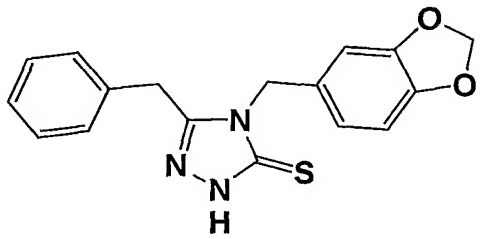


Retention time (min.) : 3.5;

Mass (ESI, Pos) : m/z 302 $(M+H)^+$.

EXAMPLE 1 (14)

5-benzyl-4-(1,3-benzodioxol-5-ylmethyl)-4H-1,2,4-triazole-3(2H)-thione

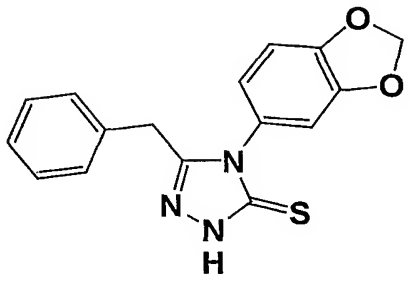


Retention time (min.) : 3.42;

Mass (ESI, Pos) : m/z 326 $(M+H)^+$.

EXAMPLE 1 (15)

5-benzyl-4-(1,3-benzodioxol-5-yl)-4H-1,2,4-triazole-3(2H)-thione

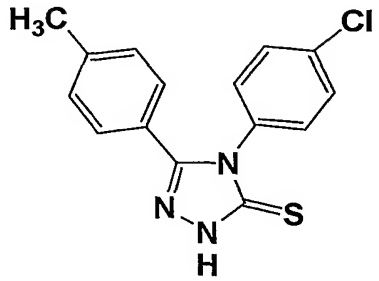


Retention time (min.) : 3.19;

Mass (ESI, Pos) : m/z 312 $(M+H)^+$.

EXAMPLE 1 (16)

5-(4-methylphenyl)-4-(4-chlorophenyl)-4H-1,2,4-triazole-3(2H)-thione

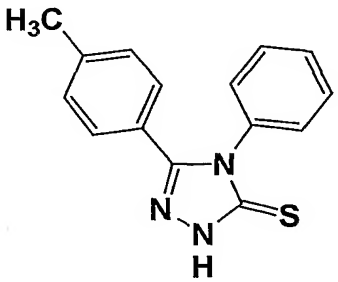


Retention time (min.) : 3.63;

Mass (ESI, Pos) : m/z 302 $(M+H)^+$.

EXAMPLE 1 (17)

5-(4-methylphenyl)-4-phenyl-4H-1,2,4-triazole-3(2H)-thione

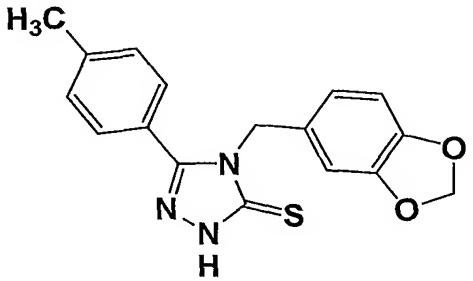


Retention time (min.) : 3.32;

Mass (ESI, Pos) : m/z 268 $(M+H)^+$.

EXAMPLE 1 (18)

5-(4-methylphenyl)-4-(1,3-benzodioxol-5-ylmethyl)-4H-1,2,4-triazole-3(2H)-thione

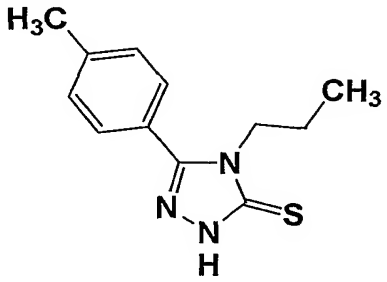


Retention time (min.) : 3.53;

Mass (ESI, Pos) : m/z 326 $(M+H)^+$.

EXAMPLE 1 (19)

5-(4-methylphenyl)-4-propyl-4H-1,2,4-triazole-3(2H)-thione

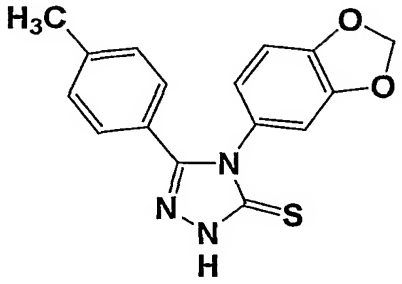


Retention time (min.) : 3.32;

Mass (ESI, Pos) : m/z 234 $(M+H)^+$.

EXAMPLE 1 (20)

5-(4-methylphenyl)-4-(1,3-benzodioxol-5-yl)-4H-1,2,4-triazole-3(2H)-thione

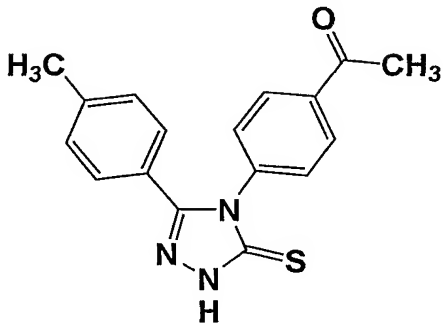


Retention time (min.) : 3.32;

Mass (ESI, Pos) : m/z 312 $(M+H)^+$.

EXAMPLE 1 (21)

5-(4-methylphenyl)-4-(4-acetylphenyl)-4H-1,2,4-triazole-3(2H)-thione

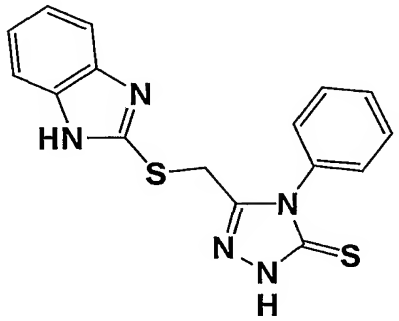


Retention time (min.) : 3.22;

Mass (ESI, Pos) : m/z 310 $(M+H)^+$.

EXAMPLE 1 (22)

5-(benzimidazol-2-ylthiomethyl)-4-phenyl-4H-1,2,4-triazole-3(2H)-thione

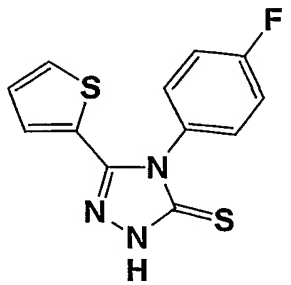


Retention time (min.) : 2.31;

Mass (ESI, Pos) : m/z 340 $(M+H)^+$.

EXAMPLE 1 (23)

5-(thiophen-2-yl)-4-(4-fluorophenyl)-4H-1,2,4-triazole-3(2H)-thione

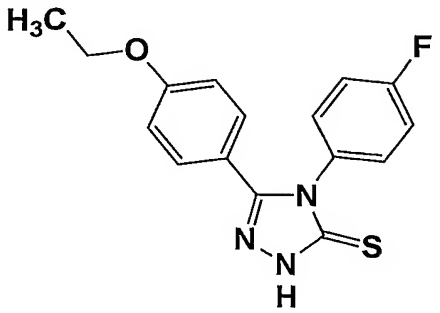


Retention time (min.) : 1.78;

Mass (ESI, Pos) : m/z 278 $(M+H)^+$.

EXAMPLE 1 (24)

5-(4-ethoxyphenyl)-4-(4-fluorophenyl)-4H-1,2,4-triazole-3(2H)-thione

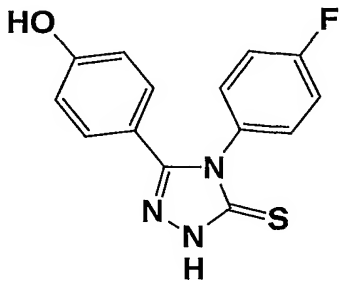


Retention time (min.) : 1.98;

Mass (ESI, Pos) : m/z 316 $(M+H)^+$.

EXAMPLE 1 (25)

5-(4-hydroxyphenyl)-4-(4-fluorophenyl)-4H-1,2,4-triazole-3(2H)-thione

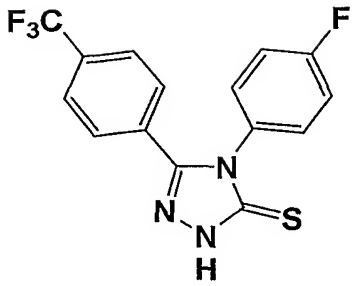


Retention time (min.) : 1.57;

Mass (ESI, Pos) : m/z 288 $(M+H)^+$.

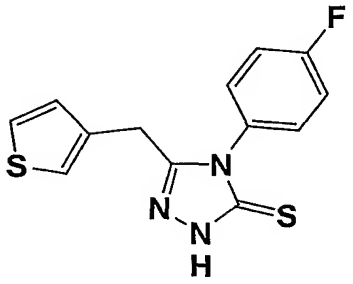
EXAMPLE 1 (26)

5-(4-trifluoromethylphenyl)-4-(4-fluorophenyl)-4H-1,2,4-triazole-3(2H)-thione



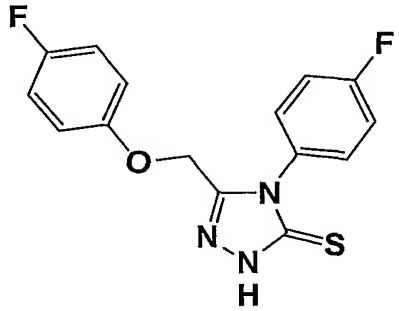
Retention time (min.) : 2.08;
Mass (ESI, Pos) : m/z 339 $(M+H)^+$.

EXAMPLE 1 (27)
5-(thiophen-3-ylmethyl)-4-(4-fluorophenyl)-4H-1,2,4-triazole-3(2H)-thione



Retention time (min.) : 1.83;
Mass (ESI, Pos) : m/z 292 $(M+H)^+$.

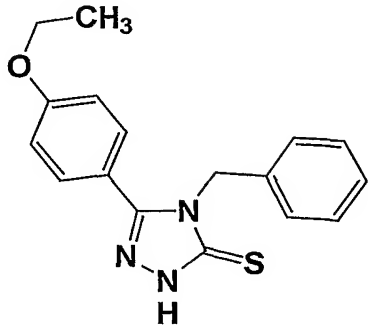
EXAMPLE 1 (28)
5-(4-fluorophenyloxymethyl)-4-(4-fluorophenyl)-4H-1,2,4-triazole-3(2H)-thione



Retention time (min.) : 1.97;
Mass (ESI, Pos) : m/z 319 $(M+H)^+$.

EXAMPLE 1 (29)

5-(4-ethoxyphenyl)-4-benzyl-4H-1,2,4-triazole-3(2H)-thione

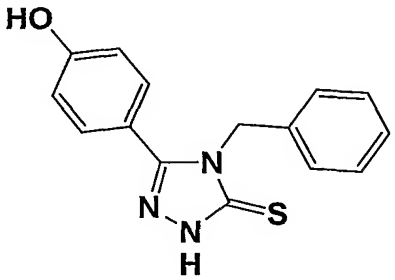


Retention time (min.) : 2.07;

Mass (ESI, Pos) : m/z 312 $(M+H)^+$.

EXAMPLE 1 (30)

5-(4-hydroxyphenyl)-4-benzyl-4H-1,2,4-triazole-3(2H)-thione

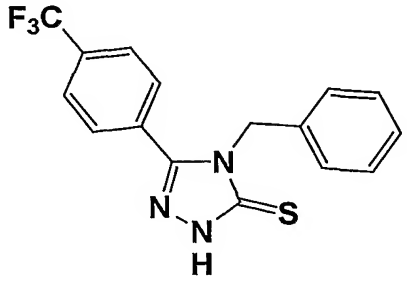


Retention time (min.) : 1.68;

Mass (ESI, Pos) : m/z 284 $(M+H)^+$.

EXAMPLE 1 (31)

5-(4-trifluoromethylphenyl)-4-benzyl-4H-1,2,4-triazole-3(2H)-thione

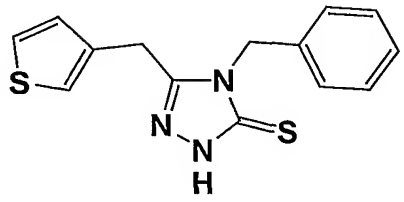


Retention time (min.) : 2.17;

Mass (ESI, Pos) : m/z 336 $(M+H)^+$.

EXAMPLE 1 (32)

5-(thiophen-3-ylmethyl)-4-benzyl-4H-1,2,4-triazole-3(2H)-thione

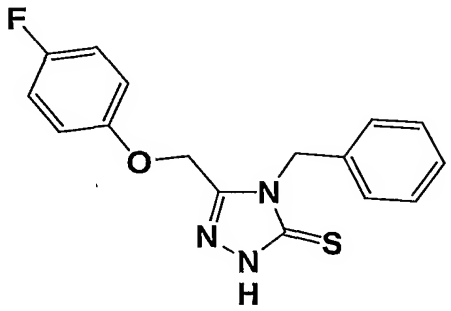


Retention time (min.) : 1.92;

Mass (ESI, Pos) : m/z 288 $(M+H)^+$.

EXAMPLE 1 (33)

5-(4-fluorophenyloxymethyl)-4-benzyl-4H-1,2,4-triazole-3(2H)-thione

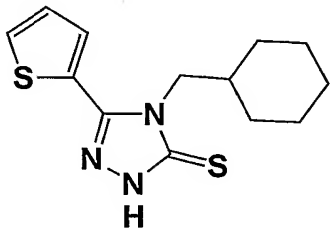


Retention time (min.) : 2.08;

Mass (ESI, Pos) : m/z 316 $(M+H)^+$.

EXAMPLE 1 (34)

5-(thiophen-2-yl)-4-cyclohexylmethyl-4H-1,2,4-triazole-3(2H)-thione

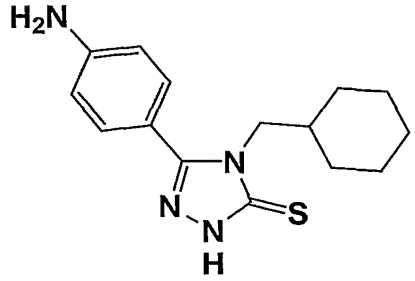


Retention time (min.) : 2.12;

Mass (ESI, Pos) : m/z 280 $(M+H)^+$.

EXAMPLE 1 (35)

5-(4-aminophenyl)-4-cyclohexylmethyl-4H-1,2,4-triazole-3(2H)-thione

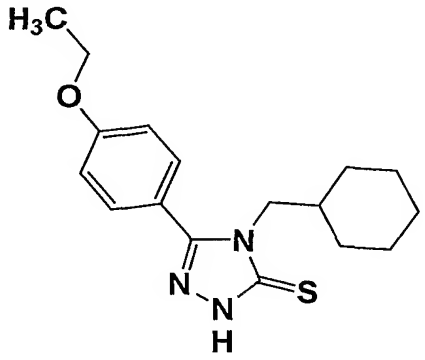


Retention time (min.) : 1.75;

Mass (ESI, Pos) : m/z 289 $(M+H)^+$.

EXAMPLE 1 (36)

5-(4-ethoxyphenyl)-4-cyclohexylmethyl-4H-1,2,4-triazole-3(2H)-thione

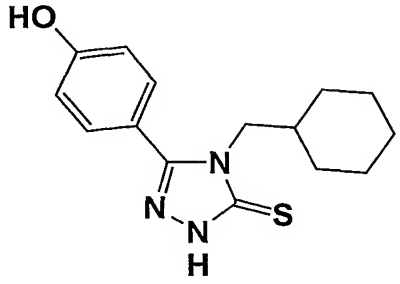


Retention time (min.) : 2.25;

Mass (ESI, Pos) : m/z 318 $(M+H)^+$.

EXAMPLE 1 (37)

5-(4-hydroxyphenyl)-4-cyclohexylmethyl-4H-1,2,4-triazole-3(2H)-thione

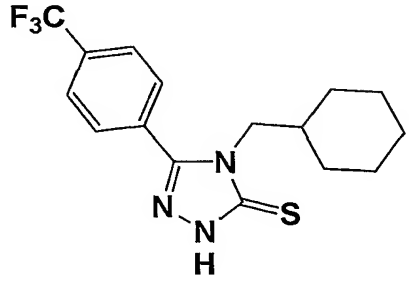


Retention time (min.) : 1.85;

Mass (ESI, Pos) : m/z 290 $(M+H)^+$.

EXAMPLE 1 (38)

5-(4-trifluoromethylphenyl)-4-cyclohexylmethyl-4H-1,2,4-triazole-3(2H)-thione

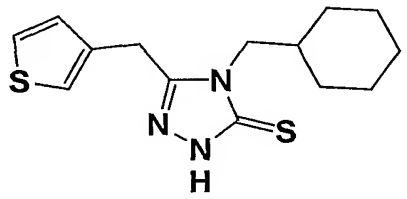


Retention time (min.) : 2.32;

Mass (ESI, Pos) : m/z 341 $(M+H)^+$.

EXAMPLE 1 (39)

5-(thiophen-3-ylmethyl)-4-cyclohexylmethyl-4H-1,2,4-triazole-3(2H)-thione

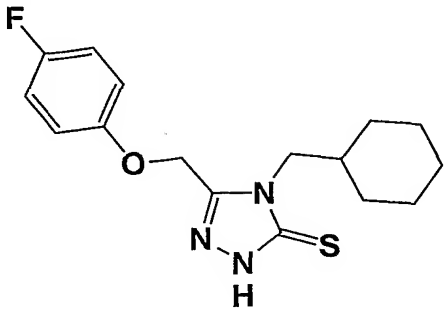


Retention time (min.) : 2.12;

Mass (ESI, Pos) : m/z 294 $(M+H)^+$.

EXAMPLE 1 (40)

5-(4-fluorophenyloxymethyl)-4-cyclohexylmethyl-4H-1,2,4-triazole-3(2H)-thione

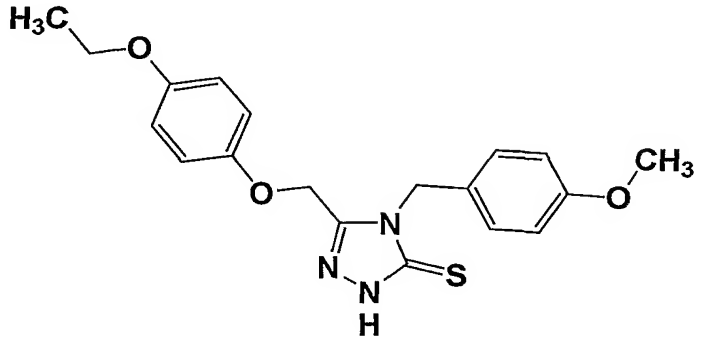


Retention time (min.) : 2.23;

Mass (ESI, Pos) : m/z 322 $(M+H)^+$.

EXAMPLE 1 (41)

5-(4-ethoxyphenyloxymethyl)-4-(4-methoxyphenylmethyl)-4H-1,2,4-triazole-3(2H)-thione

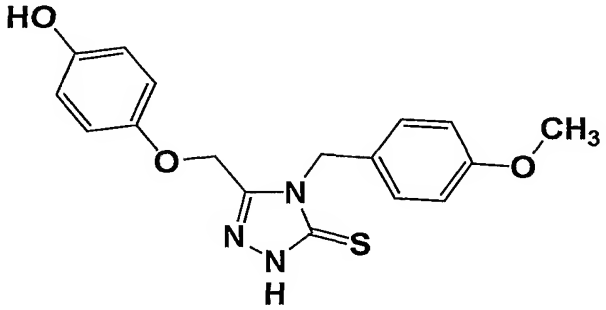


Retention time (min.) : 2.07;

Mass (ESI, Pos) : m/z 342 (M+H).

EXAMPLE 1 (42)

5-(4-hydroxyphenyloxymethyl)-4-(4-methoxyphenylmethyl)-4H-1,2,4-triazole-3(2H)-thione

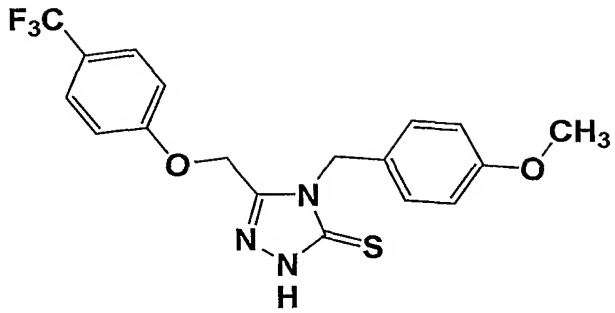


Retention time (min.) : 1.68;

Mass (ESI, Pos) : m/z 314 $(M+H)^+$.

EXAMPLE 1 (43)

5-(4-trifluoromethylphenyloxymethyl)-4-(4-methoxyphenylmethyl)-4H-1,2,4-triazole-3(2H)-thione

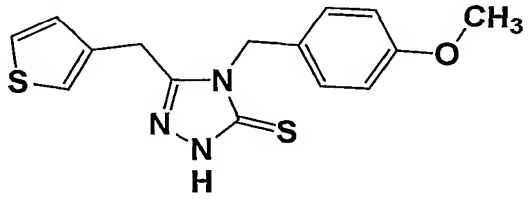


Retention time (min.) : 2.13;

Mass (ESI, Pos) : m/z 365 $(M+H)^+$.

EXAMPLE 1 (44)

5-(thiophen-3-ylmethyl)-4-(4-methoxyphenylmethyl)-4H-1,2,4-triazole-3(2H)-thione

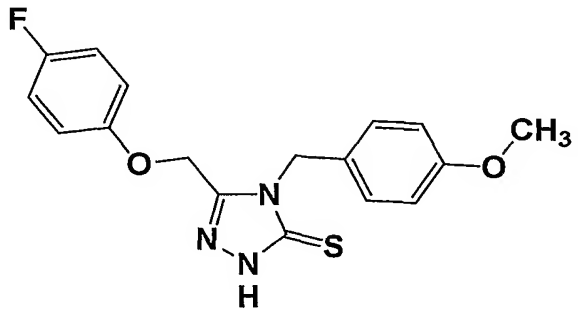


Retention time (min.) : 1.95;

Mass (ESI, Pos) : m/z 317 $(M+H)^+$.

EXAMPLE 1 (45)

5-(4-fluorophenyloxymethyl)-4-(4-methoxyphenylmethyl)-4H-1,2,4-triazole-3(2H)-thione



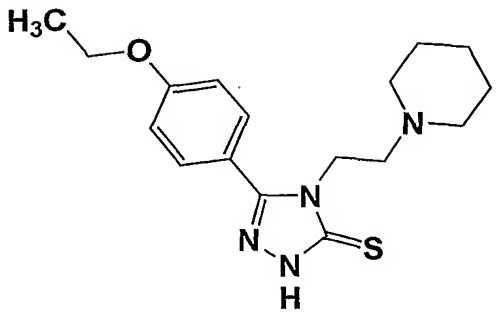
Retention time (min.) : 2.07;

Mass (ESI, Pos) : m/z 345 $(M+H)^+$.

EXAMPLE 1 (46)

5-(4-ethoxyphenyl)-4-(2-piperidinoethyl)-4H-1,2,4-triazole-

3(2H)-thione

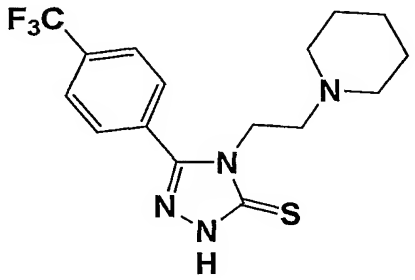


Retention time (min.) : 1.48;

Mass (ESI, Pos) : m/z 333 $(M+H)^+$.

EXAMPLE 1 (47)

5-(4-trifluoromethylphenyl)-4-(2-piperidinoethyl)-4H-1,2,4-triazole-3(2H)-thione

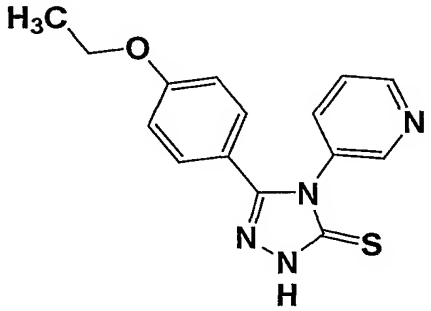


Retention time (min.) : 1.62;

Mass (ESI, Pos) : m/z 357 $(M+H)^+$.

EXAMPLE 1 (48)

5-(4-ethoxyphenyl)-4-(pyridin-3-yl)-4H-1,2,4-triazole-3(2H)-thione

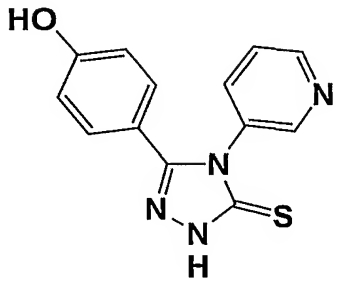


Retention time (min.) : 1.62;

Mass (ESI, Pos) : m/z 299 $(M+H)^+$.

EXAMPLE 1 (49)

5-(4-hydroxyphenyl)-4-(pyridin-3-yl)-4H-1,2,4-triazole-3(2H)-thione

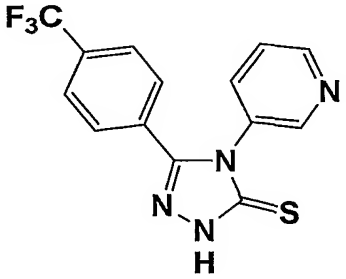


Retention time (min.) : 1.13;

Mass (ESI, Pos) : m/z 271 $(M+H)^+$.

EXAMPLE 1 (50)

5-(4-trifluoromethylphenyl)-4-(pyridin-3-yl)-4H-1,2,4-triazole-3(2H)-thione

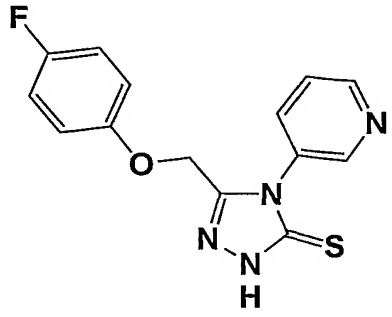


Retention time (min.) : 1.73;

Mass (ESI, Pos) : m/z 322 $(M+H)^+$.

EXAMPLE 1 (51)

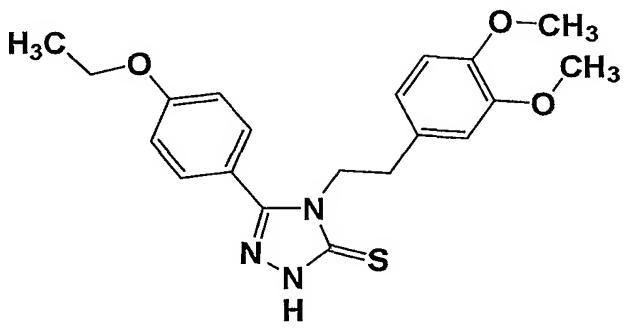
5-(4-fluorophenyloxymethyl)-4-(pyridin-3-yl)-4H-1,2,4-triazole-3(2H)-thione



Retention time (min.) : 1.58;
Mass (ESI, Pos) : m/z 303 $(M+H)^+$.

EXAMPLE 1 (52)

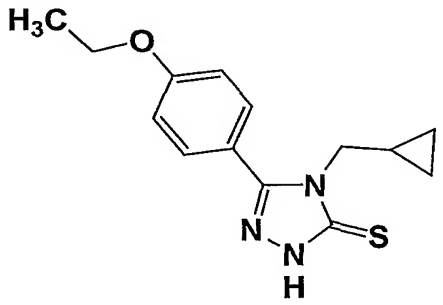
5-(4-ethoxyphenyl)-4-(2-(3,4-dimethoxyphenyl)ethyl)-4H-1,2,4-triazole-3(2H)-thione



Retention time (min.) : 1.95;
Mass (ESI, Pos) : m/z 386 $(M+H)^+$.

EXAMPLE 1 (53)

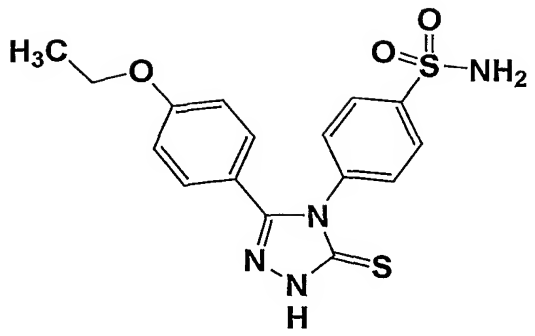
5-(4-ethoxyphenyl)-4-cyclopropylmethyl-4H-1,2,4-triazole-3(2H)-thione



Retention time (min.) : 1.95;
Mass (ESI, Pos) : m/z 276 $(M+H)^+$.

EXAMPLE 1 (54)

5-(4-ethoxyphenyl)-4-(4-aminosulfonylphenyl)-4H-1,2,4-triazole-3(2H)-thione

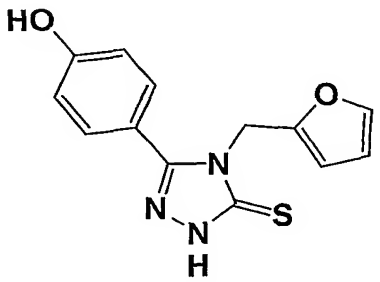


Retention time (min.) : 1.65;

Mass (ESI, Pos) : m/z 376 $(M+H)^+$.

EXAMPLE 1 (55)

5-(4-hydroxyphenyl)-4-(furan-2-ylmethyl)-4H-1,2,4-triazole-3(2H)-thione

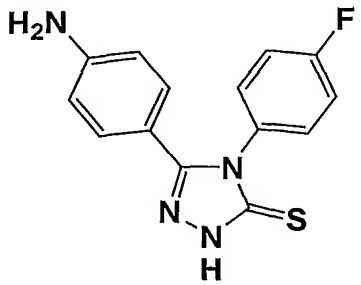


Retention time (min.) : 1.33;

Mass (ESI, Pos) : m/z 274 $(M+H)^+$.

EXAMPLE 1 (56)

5-(4-aminophenyl)-4-(4-fluorophenyl)-4H-1,2,4-triazole-3(2H)-thione

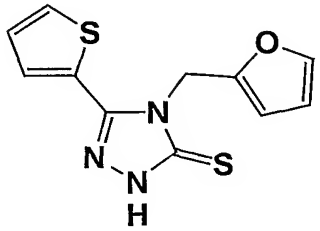


Retention time (min.) : 1.25;

Mass (ESI, Pos) : m/z 287 $(M+H)^+$.

EXAMPLE 1 (57)

5-(thiophen-2-yl)-4-(furan-2-ylmethyl)-4H-1,2,4-triazole-3(2H)-thione

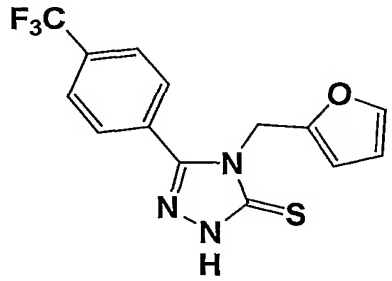


Retention time (min.) : 1.58;

Mass (ESI, Pos) : m/z 264 $(M+H)^+$.

EXAMPLE 1 (58)

5-(4-trifluoromethylphenyl)-4-(furan-2-ylmethyl)-4H-1,2,4-triazole-3(2H)-thione

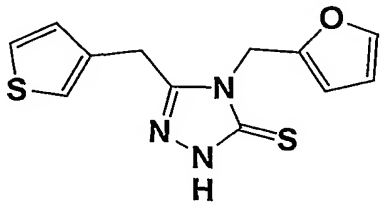


Retention time (min.) : 1.9;

Mass (ESI, Pos) : m/z 326 $(M+H)^+$.

EXAMPLE 1 (59)

5-(thiophen-3-ylmethyl)-4-(furan-2-ylmethyl)-4H-1,2,4-triazole-3(2H)-thione



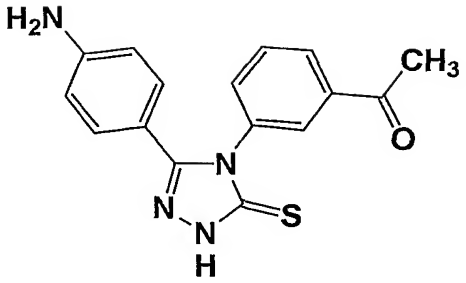
Retention time (min.) : 1.62;

Mass (ESI, Pos) : m/z 278 $(M+H)^+$.

EXAMPLE 1 (60)

5-(4-aminophenyl)-4-(3-acetylphenyl)-4H-1,2,4-triazole-

3(2H)-thione

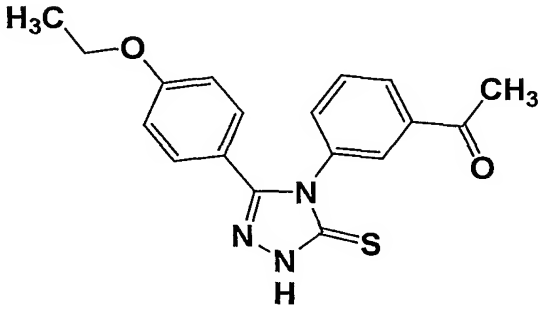


Retention time (min.) : 1.15;

Mass (ESI, Pos) : m/z 311 $(M+H)^+$.

EXAMPLE 1 (61)

5-(4-ethoxyphenyl)-4-(3-acetylphenyl)-4H-1,2,4-triazole-3(2H)-thione

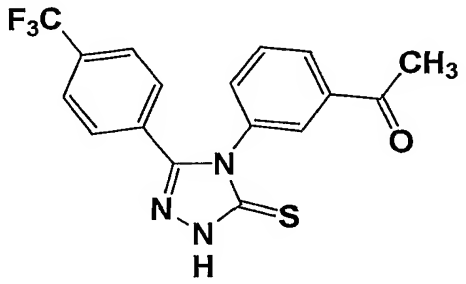


Retention time (min.) : 1.72;

Mass (ESI, Pos) : m/z 340 $(M+H)^+$.

EXAMPLE 1 (62)

5-(4-trifluoromethylphenyl)-4-(3-acetylphenyl)-4H-1,2,4-triazole-3(2H)-thione

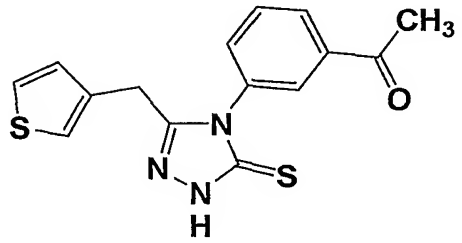


Retention time (min.) : 1.83;

Mass (ESI, Pos) : m/z 364 $(M+H)^+$.

EXAMPLE 1 (63)

5-(thiophen-3-ylmethyl)-4-(3-acetylphenyl)-4H-1,2,4-triazole-3(2H)-thione

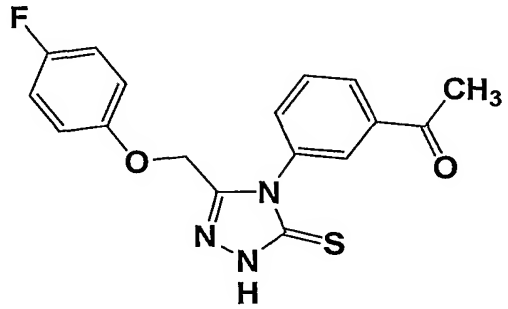


Retention time (min.) : 1.53;

Mass (ESI, Pos) : m/z 316 $(M+H)^+$.

EXAMPLE 1 (64)

5-(4-fluorophenyloxymethyl)-4-(3-acetylphenyl)-4H-1,2,4-triazole-3(2H)-thione

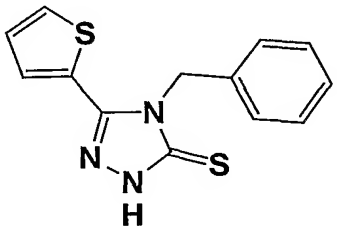


Retention time (min.) : 1.7;

Mass (ESI, Pos) : m/z 344 $(M+H)^+$.

EXAMPLE 1 (65)

5-(thiophen-2-yl)-4-benzyl-4H-1,2,4-triazole-3(2H)-thione

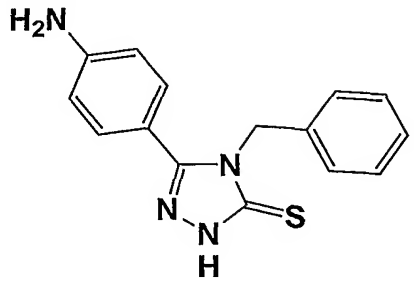


Retention time (min.) : 1.75;

Mass (ESI, Pos) : m/z 274 $(M+H)^+$.

EXAMPLE 1 (66)

5-(4-aminophenyl)-4-benzyl-4H-1,2,4-triazole-3(2H)-thione

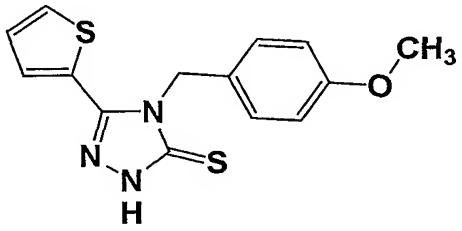


Retention time (min.) : 1.4;

Mass (ESI, Pos) : m/z 283 $(M+H)^+$.

EXAMPLE 1 (67)

5-(thiophen-2-yl)-4-(4-methyloxyphenylmethyl)-4H-1,2,4-triazole-3(2H)-thione

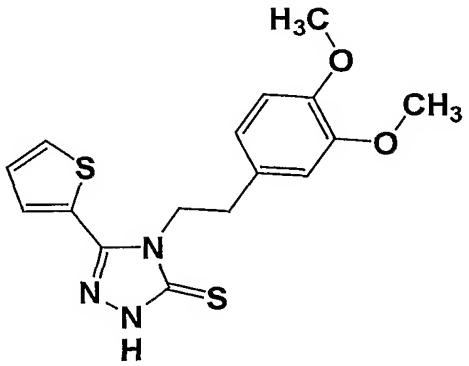


Retention time (min.) : 1.83;

Mass (ESI, Pos) : m/z 304 $(M+H)^+$.

EXAMPLE 1 (68)

5-(thiophen-2-yl)-4-(2-(3,4-dimethoxyphenyl)ethyl)-4H-1,2,4-triazole-3(2H)-thione

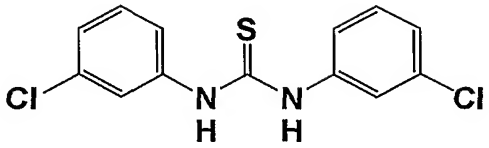


Retention time (min.) : 1.75;

Mass (ESI, Pos) : m/z 348 $(M+H)^+$.

Reference Example 2

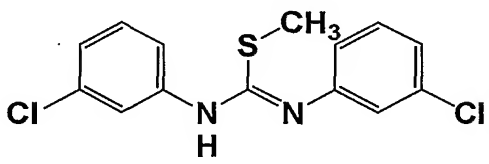
N,N'-bis(3-chlorophenyl)thiourea



To a solution of 3-chloroaniline (38 mg, 0.30 mmol) in THF (1.5 ml) 3-chlorophenylisothiocyanate (53 mg, 0.31 mmol) was added. The reaction mixture was stirred at room temperature for 16 hours. The reaction mixture was concentrated to provide the crude title compound and the residue was subsequently used without further purification.

Reference Example 3

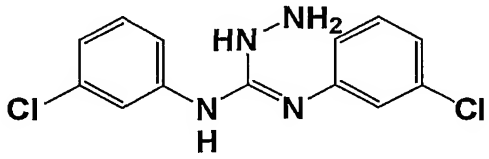
N^1,N^2-bis(3-chlorophenyl)amidinomethylsulfide



The compound prepared in reference example 2 (crude, 0.15 mmol) was dissolved in THF (1.5 ml) and to this was added methyl iodide (31 mg, 0.22 mmol). The reaction mixture was stirred for 3 hours at room temperature. The reaction mixture was concentrated to provide the title compound and the residue was used without further purification.

Reference Example 4

1-amino-2,3-bis(3-chlorophenyl) guanidine

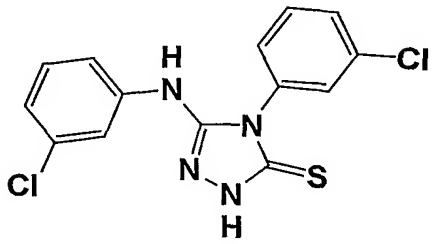


The compound prepared in reference example 3 (crude, 0.15 mmol) was dissolved in 2-propanol (1.5 ml) and to this was added hydrazine (0.22ml, 0.22 mmol, 1M solution in tetrahydrofuran). The reaction mixture was stirred at room temperature for 16 hours.

The reaction mixture was concentrated to give the title compound. The crude compound was used without further purification.

EXAMPLE 2

5-(3-chlorophenylamino)-4-(3-chlorophenyl)-4H-1,2,4-triazole-3(2H)-thione



The compound prepared in reference example 4 (crude, 0.15 mmol) was dissolved in dimethylacetamide (1.5 ml) and the solution was observed to become light blue in color. Thereto was added carbon disulfide (22 mg, 0.30 mmol) and the mixture was stirred at 130 ℃ for 4 hours. The mixture was concentrated and the desired compound was subsequently purified by LC/MS chromatography to give the compound of the present invention (27 mg).

Retention time (min.) : 3.47;

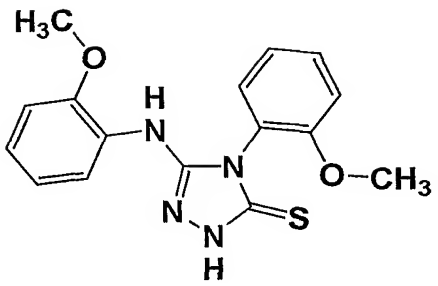
Mass (ESI, Pos) : m/z : 337 $(M+H)^+$.

EXAMPLE 2 (1) ~ EXAMPLE 2 (6)

By the same procedure as described in Reference Example 2 → Reference Example 3 → Reference Example 4 → Example 2, using the corresponding compounds in place of 3-chlorophenylamine and 3-chlorophenylthioisocyanate, the following compounds of the present invention were obtained.

EXAMPLE 2 (1)

5-(2-methoxyphenylamino)-4-(2-methoxyphenyl)-4H-1,2,4-triazole-3(2H)-thione

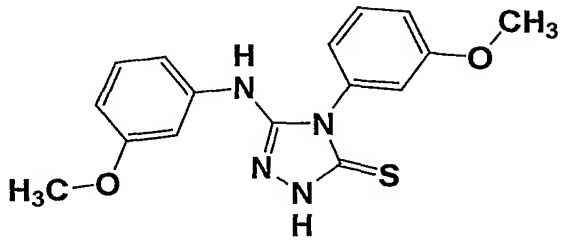


Retention time (min.) : 3.16;

Mass (ESI, Pos) : m/z : 329 $(M+H)^+$.

EXAMPLE 2 (2)

5-(3-methoxyphenylamino)-4-(3-methoxyphenyl)-4H-1,2,4-triazole-3(2H)-thione

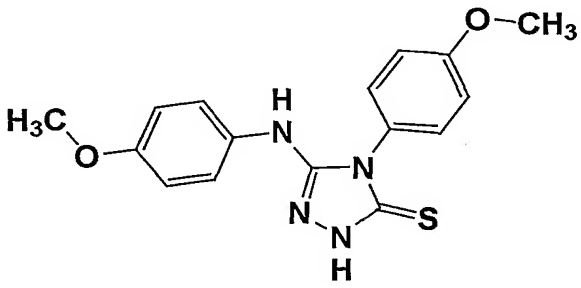


Retention time (min.) : 3.09;

Mass (ESI, Pos) : m/z : 329 $(M+H)^+$.

EXAMPLE 2 (3)

5-(4-methoxyphenylamino)-4-(4-methoxyphenyl)-4H-1,2,4-triazole-3(2H)-thione



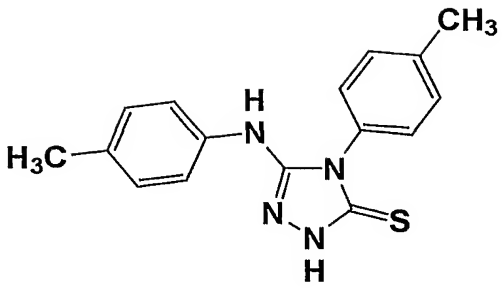
Retention time (min.) : 2.97;

Mass (ESI, Pos) : m/z : 329 $(M+H)^+$.

EXAMPLE 2 (4)

5-(4-methylphenylamino)-4-(4-methylphenyl)-4H-1,2,4-

triazole-3(2H)-thione

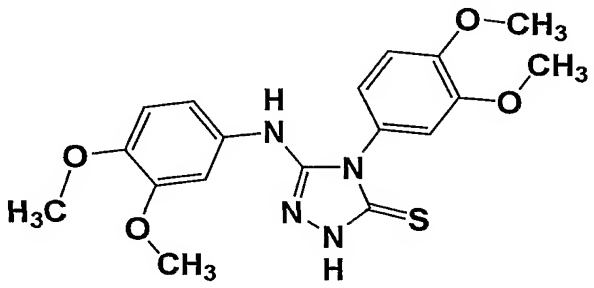


Retention time (min.) : 3.30;

Mass (ESI, Pos) : m/z : 297 $(M+H)^+$.

EXAMPLE 2 (5)

5-(3,4-dimethoxyphenylamino)-4-(3,4-dimethoxyphenyl)-4H-1,2,4-triazole-3(2H)-thione

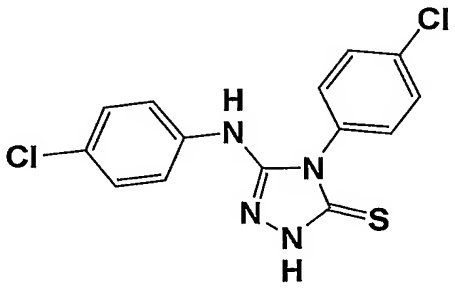


Retention time (min.) : 2.68;

Mass (ESI, Pos) : m/z : 389 $(M+H)^+$.

EXAMPLE 2 (6)

5-(4-chlorophenylamino)-4-(4-chlorophenyl)-4H-1,2,4-triazole-3(2H)-thione



Retention time (min.) : 3.52;

Mass (ESI, Pos) : m/z : 337 $(M+H)^+$.

[Formulation Example]

Formulation Example 1

The following components were admixed in a conventional method and punched out to give 100 tablets each containing 100 mg of active ingredient.

- 5-(3-chlorophenylamino)-4-(3-chlorophenyl)-4H-1,2,4-triazole-3(2H)-thione ••••••10.0 g
- carboxymethylcellulose calcium (disintegrating agent) ••••••0.2 g
- Magnesium stearate (Lubricating agent) ••••••0.1 g
- Microcrystaline cellulose ••••••9.7 g

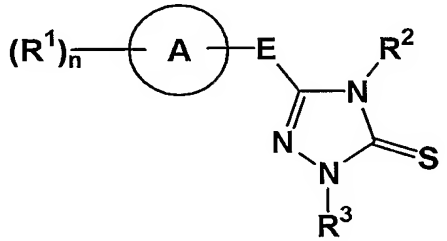
Formulation Example 2

The following components were admixed in a conventional method. The solution was sterilized in a conventional method, placed 5 ml portions into ampoules and freezedried to give 100 ampoules each containing 20 mg of active ingredient.

- 5-(3-chlorophenylamino)-4-(3-chlorophenyl)-4H-1,2,4-triazole-3(2H)-thione ••••••2 g
- mannitol ••••••5 g
- distilled water ••••••1000 ml

CLAIMS

1. A method for prevention and/or treatment of diseases induced by activation of neutral sphingomyelinase, which comprises the administration of an effective amount of a compound of formula (I)



(I)

,

wherein

R^1 is C1-6 alkyl, C1-6 alkoxy, phenyl, hydroxy, amino, halogen, trifluoromethyl or trifluoromethyloxy;

A is a C3-10 mono- or bi-cyclic carbon ring or a 4-10 membered mono- or bi-cyclic hetero ring containing 1-3 of nitrogen, oxygen and/or sulfur,

E is a bond, C1-6 alkylene (one of carbon atom may be replaced by oxygen or sulfur, with the proviso that the carbon atom attached to triazoline ring is not replaced) or $-NR^4-$,

R^2 is hydrogen, C1-6 alkyl, C2-6 alkenyl, C2-6 alkynyl or C1-4 alkyl substituted by 1-3 of C3-10 mono- or bi-cyclic carbon ring or 4-10 membered hetero ring containing 1-3 of nitrogen, oxygen and/or sulfur,

Said carbon ring or hetero ring in R^2 may be substituted by C1-6 alkyl, C1-6 alkoxy, $SO_2NR^6R^7$, C2-6 acyl or halogen;

R^3 is hydrogen or C1-4 hydroxyalkyl;

n=0~5;

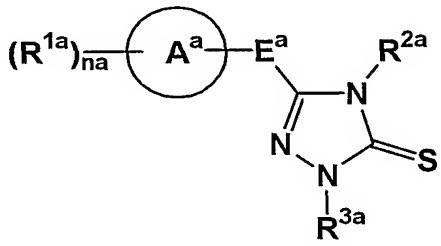
R^4 is hydrogen or C1-4 alkyl;

R^5 and R^6 are the same or different to represent hydrogen or C1-4 alkyl or R^5 and R^6 are taken together to form C3-6 alkylene],

a non-toxic salt thereof or a hydrate thereof as active ingredient.

2. A method according to claim 1, wherein the diseases induced by activation of neutral sphingomyelinase are arteriosclerosis, cerebral ischemia, cardiac ischemia, lung injury, renal injury, GVHD, transplant rejection or HIV.

3. A compound of formula (Ia)



(Ia)

,

wherein R^{1a} is C1-6 alkyl, C1-6 alkoxy, phenyl, hydroxy, amino, halogen, trifluoromethyl or trifluoromethyloxy;

A^a is a C3-10 mono- or bi-cyclic carbon ring or a 4-10 membered mono- or bi-cyclic hetero ring containing 1-3 of nitrogen, oxygen and/or sulfur atom(s),

E^a is a bond, C1-6 alkylene (one of carbon atom may be replaced by oxygen or sulfur atom, with the proviso that the carbon atom attached to triazoline ring is not replaced) or $-NR^4-$,

R^{2a} is hydrogen, C1-6 alkyl, C2-6 alkenyl, C2-6 alkynyl, C1-4 alkyl substituted by 1-3 of C3-10 mono- or bi-cyclic carbon ring or 4-10 membered hetero ring containing 1-3 of nitrogen, oxygen and/or sulfur atom(s),

Said carbon ring or hetero ring in R^2 may be substituted by C1-6 alkyl, C1-6 alkoxy, $SO_2NR^6R^7$ or C2-6 acyl or halogen;

R^{3a} is hydrogen or C1-4 hydroxyalkyl;

n^a is 0 or an integer of 1 ~ 5;

R^{4a} is hydrogen or C1-4 alkyl;

R^{5a} and R^{6a} are the same or different to represent hydrogen, C1-4 alkyl, or R^{5a} and R^{6a} are taken together to form C3-6 alkylene), a non-toxic salt thereof or a hydrate thereof,

with the proviso that the following compounds (i) ~ (xxxiii) are excluded;

(i) 5-benzyl-4-phenyl-4H-1,2,4-triazole-3(2H)-thione,

(ii) 5-(5-chloro-2-hydroxyphenyl)-4-phenyl-4H-1,2,4-triazole-3(2H)-thione,

(iii) 5-(1-(2-phenylphenoxy)ethyl)-4-phenyl-4H-1,2,4-triazole-3(2H)-thione,

(iv) 5-(1-(4-chlorophenoxy)ethyl)-4-ethyl-4H-1,2,4-triazole-3(2H)-thione,

(v) 5-(1-(4-chloro-2-methylphenoxymethyl)-4-(2-propenyl)-4H-1,2,4-triazole-3(2H)-thione,

(vi) 5-(5-chloro-2-hydroxyphenyl)-4-methyl-4H-1,2,4-triazole-3(2H)-thione,

(vii) 5-(4-trifluoromethyloxyphenoxylmethyl)-4-(1-methyl ethyl)-4H-1,2,4-triazole-3(2H)-thione,

(viii) 5-(4-trifluoromethyloxyphenoxylmethyl)-4-(4-chlorophenyl)-4H-1,2,4-triazole-3(2H)-thione,

(ix) 5-(2-chlorophenyl)-4-phenyl-4H-1,2,4-triazole-3(2H)-thione,

(x) 5-(4-bromophenoxymethyl)-4-phenyl-4H-1,2,4-triazole-3(2H)-thione,

(xi) 5-(4-bromo-3,5-dimethylphenoxymethyl)-4-phenyl-4H-1,2,4-triazole-3(2H)-thione,

(xii) 5-(4-chloro-2-methylphenoxymethyl)-4-phenyl-4H-1,2,4-triazole-3(2H)-thione,

(xiii) 5-(indol-3-ylmethyl)-4-phenyl-4H-1,2,4-triazole-3(2H)-thione,

(xiv) 5-(2,3-dichlorophenoxymethyl)-4-phenyl-4H-1,2,4-triazole-3(2H)-thione,

(xv) 5-(2,4-dimethylphenoxymethyl)-4-phenyl-4H-1,2,4-triazole-3(2H)-thione,

(xvi) 5-(3,4,5-trimethoxyphenyloxymethyl)-4-phenyl-4H-1,2,4-triazole-3(2H)-thione,

(xvii) 5-(1-(4-chlorophenylthio)ethyl)-4-phenyl-4H-1,2,4-triazole-3(2H)-thione,

(xviii) 5-pyridin-4-yl-4-(3-methyl-4-(1-methylethyl)phenyl)-4H-1,2,4-triazole-3(2H)-thione,

(xix) 5-(6-bromonaphthalen-2-yloxymethyl)-4-phenyl-4H-1,2,4-triazole-3(2H)-thione,

(xx) 5-(2-chloro-5-methylphenyloxymethyl)-4-phenyl-4H-1,2,4-triazole-3(2H)-thione,

(xxi) 5-(3,5-bis(trifluoromethyl)phenyl)-4H-1,2,4-triazole-3(2H)-thione,

(xxii) 5-(4-t-butylphenyl)-4H-1,2,4-triazole-3(2H)-thione,

(xxiii) 5-phenyl-4H-1,2,4-triazole-3(2H)-thione,

(xxiv) 5-(thiophen-2-yl)-4-phenyl-4H-1,2,4-triazole-3(2H)-thione,

(xxv) 5-(2,3,4,5,6-tetramethylphenylmethylthiomethyl)-4-(4-fluorophenyl)-4H-1,2,4-triazole-3(2H)-thione,

(xxvi) 5-(2-chlorophenyl)-4-(2-methylphenyl)-4H-1,2,4-triazole-3(2H)-thione,

(xxvii) 5-(furan-2-yl)-4-(2-chlorophenyl)-4H-1,2,4-triazole-3(2H)-thione,

(xxviii) 5-(furan-2-yl)-4-(4-methoxyphenyl)-4H-1,2,4-triazole-3(2H)-thione,

(xxix) 5-(3,4,5-trimethoxyphenyl)-4-(4-methoxyphenyl)-4H-1,2,4-triazole-3(2H)-thione,

(xxx) 5-(furan-2-yl)-4-(4-chlorophenyl)-4H-1,2,4-triazole-3(2H)-thione,

(xxxi) 5-(furan-2-yl)-4-phenyl-4H-1,2,4-triazole-3(2H)-thione,

(xxxii) 5-phenylamino-4-phenyl-4H-1,2,4-triazole-3(2H)-thione,

(xxxiii) 5-(2-bromophenylamino)-4-(2-bromophenyl)-4H-1,2,4-triazole-3(2H)-thione,

(xxxiv) 5-phenylamino-4-phenyl-2-hydroxymethyl-4H-1,2,4-triazole-3(2H)-thione.

4. A compound according to claim 3, of formula (Ia) wherein E is NR^5, a non-toxic salt thereof or hydrate thereof.

5. A compound according to claim 3, of formula (Ia) wherein E is a bond or C1-6 alkylene (one of carbon atom may be replaced by oxygen or sulfur atom, with the proviso that the carbon atom attached to triazoline ring is not replaced), a non-toxic salt thereof or a hydrate thereof.

6. A compound according to claim 3, which is

(1) 5-(4-methoxyphenyl)-4-phenyl-4H-1,2,4-triazole-3(2H)-thione,

(2) 5-(thiophen-2-yl)-4-(4-chlorophenyl)-4H-1,2,4-triazole-3(2H)-thione,

(3) 5-(thiophen-2-yl)-4-(1,3-dioxaindan-5-ylmethyl)-4H-1,2,4-triazole-3(2H)-thione,

(4) 5-(thiophen-2-yl)-4-propyl-4H-1,2,4-triazole-3(2H)-thione,

(5) 5-(thiophen-2-yl)-4-(4-methoxyphenyl)-4H-1,2,4-triazole-3(2H)-thione,

(6) 5-(thiophen-2-yl)-4-(1,3-dioxaindan-5-yl)-4H-1,2,4-triazole-3(2H)-thione,

(7) 5-(4-methoxyphenyl)-4-(1,3-dioxaindan-5-ylmethyl)-4H-1,2,4-triazole-3(2H)-thione,

(8) 5-(4-methoxyphenyl)-4-propyl-4H-1,2,4-triazole-3(2H)-thione,

(9) 5-(4-methoxyphenyl)-4-(4-piperidinosulfonylphenyl)-4H-1,2,4-triazole-3(2H)-thione,

(10) 5-(4-methoxyphenyl)-4-(4-methoxyphenyl)-4H-1,2,4-triazole-3(2H)-thione,

(11) 5-(4-methoxyphenyl)-4-(1,3-dioxaindan-5-yl)-4H-1,2,4-triazole-3(2H)-thione,

(12) 5-(furan-2-yl)-4-(1,3-dioxaindan-5-ylmethyl)-4H-1,2,4-triazole-3(2H)-thione,

(13) 5-(furan-2-yl)-4-(1,3-dioxaindan-5-yl)-4H-1,2,4-triazole-3(2H)-thione,

(14) 5-benzyl-4-(4-chlorophenyl)-4H-1,2,4-triazole-3(2H)-thione,

(15) 5-benzyl-4-(1,3-dioxaindan-5-ylmethyl)-4H-1,2,4-triazole-3(2H)-thione,

(16) 5-benzyl-4-(1,3-dioxaindan-5-yl)-4H-1,2,4-triazole-3(2H)-thione,

(17) 5-(4-methylphenyl)-4-(4-chlorophenyl)-4H-1,2,4-triazole-3(2H)-thione,

(18) 5-(4-methylphenyl)-4-phenyl-4H-1,2,4-triazole-3(2H)-thione,

(19) 5-(4-methylphenyl)-4-(1,3-dioxaindan-5-ylmethyl)-4H-1,2,4-triazole-3(2H)-thione,

(20) 5-(4-methylphenyl)-4-propyl-4H-1,2,4-triazole-3(2H)-thione,

(21) 5-(4-methylphenyl)-4-(1,3-dioxaindan-5-yl)-4H-1,2,4-triazole-3(2H)-thione,

(22) 5-(4-methylphenyl)-4-(4-acetylphenyl)-4H-1,2,4-triazole-3(2H)-thione,

(23) 5-(benzimidazol-2-ylthiomethyl)-4-phenyl-4H-1,2,4-triazole-3(2H)-thione,

(24) 5-(thiophen-2-yl)-4-(4-fluorophenyl)-4H-1,2,4-triazole-3(2H)-thione,

(25) 5-(4-ethoxyphenyl)-4-(4-fluorophenyl)-4H-1,2,4-triazole-3(2H)-thione,

(26) 5-(4-hydroxyphenyl)-4-(4-fluorophenyl)-4H-1,2,4-triazole-3(2H)-thione,

(27) 5-(4-trifluoromethylphenyl)-4-(4-fluorophenyl)-4H-1,2,4-triazole-3(2H)-thione,

(28) 5-(thiophen-3-ylmethyl)-4-(4-fluorophenyl)-4H-1,2,4-triazole-3(2H)-thione,

(29) 5-(4-fluorophenyloxymethyl)-4-(4-fluorophenyl)-4H-1,2,4-triazole-3(2H)-thione,

(30) 5-(4-ethoxyphenyl)-4-benzyl-4H-1,2,4-triazole-3(2H)-thione,

(31) 5-(4-hydroxyphenyl)-4-benzyl-4H-1,2,4-triazole-3(2H)-thione,

(32) 5-(4-trifluoromethylphenyl)-4-benzyl-4H-1,2,4-triazole-3(2H)-thione,

(33) 5-(thiophen-3-ylmethyl)-4-benzyl-4H-1,2,4-triazole-3(2H)-thione,

(34) 5-(4-fluorophenyloxymethyl)-4-benzyl-4H-1,2,4-triazole-3(2H)-thione,

(35) 5-(thiophen-2-yl)-4-cyclohexylmethyl-4H-1,2,4-triazole-3(2H)-thione,

(36) 5-(4-aminophenyl)-4-cyclohexylmethyl-4H-1,2,4-triazole-3(2H)-thione,

(37) 5-(4-ethoxyphenyl)-4-cyclohexylmethyl-4H-1,2,4-triazole-3(2H)-thione,

(38) 5-(4-hydroxyphenyl)-4-cyclohexylmethyl-4H-1,2,4-triazole-3(2H)-thione,

(39) 5-(4-trifluoromethylphenyl)-4-cyclohexylmethyl-4H-1,2,4-triazole-3(2H)-thione,

(40) 5-(thiophen-3-ylmethyl)-4-cyclohexylmethyl-4H-1,2,4-triazole-3(2H)-thione,

(41) 5-(4-fluorophenyloxymethyl)-4-cyclohexylmethyl-4H-1,2,4-triazole-3(2H)-thione,

(42) 5-(4-ethoxyphenyloxymethyl)-4-(4-methoxyphenylmethyl)-4H-1,2,4-triazole-3(2H)-thione,

(43) 5-(4-hydroxyphenyloxymethyl)-4-(4-methoxyphenylmethyl)-4H-1,2,4-triazole-3(2H)-thione,

(44) 5-(4-trifluoromethylphenyl)-4-(4-methoxyphenylmethyl)-4H-1,2,4-triazole-3(2H)-thione,

(45) 5-(thiophen-3-ylmethyl)-4-(4-methoxyphenylmethyl)-4H-1,2,4-triazole-3(2H)-thione,

(46) 5-(4-fluorophenyloxymethyl)-4-(4-methoxyphenylmethyl)-4H-1,2,4-triazole-3(2H)-thione,

(47) 5-(4-ethoxyphenyl)-4-(2-piperidinoethyl)-4H-1,2,4-triazole-3(2H)-thione,

(48) 5-(4-trifluoromethylphenyl)-4-(2-piperidinoethyl)-4H-1,2,4-triazole-3(2H)-thione,

(49) 5-(4-ethoxyphenyl)-4-(pyridin-3-yl)-4H-1,2,4-triazole-3(2H)-thione,

(50) 5-(4-hydroxyphenyl)-4-(pyridin-3-yl)-4H-1,2,4-triazole-3(2H)-thione,

(51) 5-(4-trifluoromethylphenyl)-4-(pyridin-3-yl)-4H-1,2,4-triazole-3(2H)-thione,

(52) 5-(4-fluorophenyloxymethyl)-4-(pyridin-3-yl)-4H-1,2,4-triazole-3(2H)-thione,

(53) 5-(4-ethoxyphenyl)-4-(2-(3,4-dimethoxyphenyl)ethyl)-4H-1,2,4-triazole-3(2H)-thione,

(54) 5-(4-ethoxyphenyl)-4-cyclopropylmethyl-4H-1,2,4-triazole-3(2H)-thione,

(55) 5-(4-ethoxyphenyl)-4-(4-aminosulfonylphenyl)-4H-1,2,4-triazole-3(2H)-thione,

(56) 5-(4-hydroxyphenyl)-4-(furan-2-ylmethyl)-4H-1,2,4-triazole-3(2H)-thione,

(57) 5-(4-aminophenyl)-4-(4-fluorophenyl)-4H-1,2,4-triazole-3(2H)-thione,

(58) 5-(thiophen-2-yl)-4-(furan-2-ylmethyl)-4H-1,2,4-triazole-3(2H)-thione,

(59) 5-(4-trifluoromethylphenyl)-4-(furan-2-ylmethyl)-4H-1,2,4-triazole-3(2H)-thione,

(60) 5-(thiophen)-3-il4-(furan-2-ylmethyl)-4H-1,2,4-triazole-3(2H)-thione,

(61) 5-(4-aminophenyl)-4-(3-acetylphenyl)-4H-1,2,4-triazole-3(2H)-thione,

(62) 5-(4-ethoxyphenyl)-4-(3-acetylphenyl)-4H-1,2,4-triazole-3(2H)-thione,

(63) 5-(4-trifluoromethylphenyl)-4-(3-acetylphenyl)-4H-1,2,4-triazole-3(2H)-thione,

(64) 5-(thiophen-3-ylmethyl)-4-(3-acetylphenyl)-4H-1,2,4-triazole-3(2H)-thione,

(65) 5-(4-fluorophenyloxymethyl)- 4H-1,2,4-triazole-3(2H)-thione,
(66) 5-(thiophen-2-yl)-4-benzyl-4H-1,2,4-triazole-3(2H)-thione,
(67) 5-(4-aminophenyl)-4-benzyl-4H-1,2,4-triazole-3(2H)-thione,
(68) 5-(thiophen-2-yl)-4-(4-methyloxyphenylethyl)-4H-1,2,4-triazole-3(2H)-thione or
(69) 5-(thiophen-2-yl)-4-(2-(3,4-dimethoxyphenyl)ethyl)-4H-1,2,4-triazole-3(2H)-thione.

7. A compound according to claim 3, which is
(1) 5-(3-chlorophenylamino)-4-(3-chlorophenyl)-4H-1,2,4-triazole-3(2H)-thione,
(2) 5-(2-methoxyphenylamino)-4-(2-methoxyphenyl)-4H-1,2,4-triazole-3(2H)-thione,
(3) 5-(3-methoxyphenylamino)-4-(3-methoxyphenyl)-4H-1,2,4-triazole-3(2H)-thione,
(4) 5-(4-methoxyphenylamino)-4-(4-methoxyphenyl)-4H-1,2,4-triazole-3(2H)-thione,
(5) 5-(4-methylphenylamino)-4-(4-methylphenyl)-4H-1,2,4-triazole-3(2H)-thione,
(6) 5-(3,4-dimethoxyphenylamino)-4-(3,4-dimethoxyphenyl)-4H-1,2,4-triazole-3(2H)-thione or
(7) 5-(4-chlorophenylamino)-4-(4-chlorophenyl)-4H-1,2,4-triazole-3(2H)-thione.

8. A pharmaceutical composition for the prevention and/or treatment of diseases induced by activation of neutral sphingomyelinase, which comprises, as active ingredient, an effective amount of a compound of formula (I) described in claim 1.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/JP 02/01472

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07D249/12 C07D249/14 C07D405/06 C07D405/04 C07D405/14
C07D409/04 C07D409/14 C07D403/12 C07D409/06 C07D401/04
C07D403/06 A61K31/4196 A61P31/18 A61P9/10 A61P25/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07D A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, WPI Data, PAJ, BEILSTEIN Data, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

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"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
31 May 2002	13/06/2002

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Chouly, J

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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
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X	G. JAYANTHI ET AL: "Photochemical synthesis of s-triazolo'3,4-b!benzothiazole and mechanistic studies on benzothiazole formation" JOURNAL OF ORGANIC CHEMISTRY, vol. 62, no. 17, 1997, pages 5766-5770, XP002200693 EASTON US page 5766, formula 3; page 5769 ---	3-6
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